ORGANIC CHEMISTRY

A Modern Approach

Volume-III

About the Author

Nimai Tewari is retired Associate Professor in the Department of Chemistry, Katwa College (affiliated to the University of Burdwan), West Bengal. A PhD in Organic Chemistry from Calcutta University, he has taught the subject for a period of more than three decades. He has published various research papers in national and international journals. Apart from Organic Chemistry—A Modern Approach, Volume-III (including Volume-I and Volume-II of this title), Dr. Tewari has authored three more books on Organic Chemistry for undergraduate and postgraduate students. His research interest includes Organic Synthesis and Heterocyclic Chemistry.

ORGANIC CHEMISTRY

A Modern Approach

Volume-III

Nimai Tewari

Associate Professor (Retired)
Department of Chemistry
Katwa College
West Bengal

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Dedicated to

Sri Sarada Devi, the Holy Mother

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Preface

In the course of teaching Organic Chemistry at the undergraduate level, I felt constantly the need of a concise volume that dealt with important topics like synthesis, spectroscopy and biomolecules included in the final year syllabus of chemistry (Hons). Students often expressed their difficulty caused by the absence of such a book. It is the long-felt difficulty of the students that motivated me to undertake this work on organic chemistry based on modern structural theories.

This book is organised into ten chapters: (i) Nitrogen Compounds, (ii) Organometallic Compounds, (iii) The Logic of Organic Synthesis, (iv) Organic Spectroscopy, (v) Polynuclear Hydrocarbons, (vi) Heterocyclic Compounds, (vii) Stereochemistry of Alicyclic Compounds, (viii) Pericyclic Reactions, (ix) Carbohydrates, and (x) Aminoacids, Peptides, Proteins, and Nucleic Acids.

By following a modern methodology of learning, the book presents a large number of reactions with discussions supported with mechanistic explanations and diagrams, wherever needed. I believe that a fruitful way for the students to make their knowledge sound and also to acquire command over the subject is to deal with well-designed problems covering various aspects of organic chemistry. For this reason, a large number of solved as well as study problems have been included at the end of each article of every chapter of this book. It must help to develop the proficiency of the students.

I am pleased to note that Volume-I and Volume-II of this book have been received well by both teachers and students. This volume will also be highly useful and dependable guide not only to the advanced degree students of organic chemistry but also to the aspirants, preparing for various competitive examinations like NET, GATE and SLET.

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Constructive suggestions from the readers for further improvement of the book are most welcome. These can be shared at: *n.tewari54@gmail.com*.

Nimai Tewari

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Nitrogen Compounds

1

Chapter Outline

Introduction

1.1 Amines (Aliphatic and Aromatic)
  - 1.1.1 Preparations
  - 1.1.2 Distinction between Primary, Secondary and Tertiary Amines
  - 1.1.3 Separation of Primary, Secondary and Tertiary Amines by Hinsberg's Method
  - 1.1.4 Reactions
  - 1.1.5 Phenylenediamines

1.2 Diazomethane (CH_2N_2)
  - 1.2.1 Preparation of Diazomethane
  - 1.2.2 Properties and Structure of Diazomethane
  - 1.2.3 Uses of Diazomethane

1.3 Diazoacetic Ester ($N\equiv\overset{\oplus}{N}—\overset{\ominus}{C}H—CO_2Et$)
  - 1.3.1 Preparation of Diazoacetic Ester
  - 1.3.2 Structure and Properties of Diazoacetic Ester
  - 1.3.3 Uses of Diazoacetic Ester

1.4 Nitro Compounds (Aliphatic and Aromatic)
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  - 1.4.2 Reactions

1.5 Alkyl Nitriles and Isonitriles
  - 1.5.1 Preparations
  - 1.5.2 Reactions

1.6 Diazonium Salts and Their Related Compounds
  - 1.6.1 Reactions
  - 1.6.2 Synthesis Using Diazonium Salts

INTRODUCTION

The class of organic compounds having functional groups containing nitrogen is termed as 'nitrogenous organic compounds'. A large number of nitrogen containing organic compounds, isolated from natural sources, is essential for the continuation of the process of life. Amino acids and proteins are the main nitrogenous compounds that are present in all living systems.

Nitrogenous organic compounds are classified into amines, nitro compounds, nitriles, etc., on the basis of the nature of nitrogen containing functional groups. In this chapter, discussion will be restricted to amines, nitro compounds, alkyl cyanides, alkyl isocyanides and diazonium salts.

1.1 AMINES (ALIPHATIC AND AROMATIC)

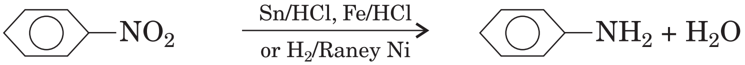
1.1.1 Preparations

1.1.1.1 Preparation of Primary Amines

1. By reduction of nitro compounds Reduction of nitro compounds by Sn/HCl, Zn/HCl, Fe/HCl, H_2/Ni or $LiAlH_4$ produces primary amines.

Examples:

$$\underset{\text{Nitromethane}}{CH_3—NO_2} \xrightarrow[\text{or } LiAlH_4]{\text{Sn/HCl or } H_2/Ni} \underset{\text{Methylamine}}{CH_3—NH_2} + H_2O$$

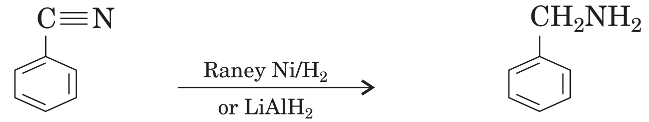


Nitrobenzene Aniline

2. By reduction of alkylcyanides or alkylnitriles When alkyl cyanides are reduced by H_2/Ni, $LiAlH_4$ or (Na + C_2H_5OH), primary amines are obtained.

Examples:

$$\underset{\text{Methyl cyanide}}{CH_3—C{\equiv}N} \xrightarrow[\text{or } (Na + C_2H_5OH)]{H_2/Ni,\ LiAlH_4} \underset{\text{Ethylamine}}{CH_3CH_2NH_2}$$

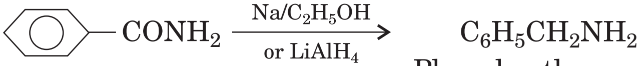


Benzonitrile Phenylmethanamine or Benzylamine

3. By reduction of acid amides When acid amides are reduced by Na/EtOH or $LiAlH_4$, primary amines are obtained.

Examples:

$$\underset{\text{Acetamide}}{CH_3CONH_2} \xrightarrow[\text{or } LiAlH_4]{Na/C_2H_5OH} \underset{\text{Ethylamine}}{CH_3CH_2NH_2}$$



Benzamide

$C_6H_5CH_2NH_2$

Phenylmethanamine or Benzylamine

4. By reduction of aldoximes or ketoximes Aldoximes or ketoximes are reduced by Na/C_2H_5OH or $LiAlH_4$ to give primary amines.

Examples:

$$\underset{\text{Acetaldehyde oxime}}{CH_3CH{=}NOH} \xrightarrow[\text{or } LiAlH_4]{Na/C_2H_5OH} \underset{\text{Ethylamine}}{CH_3CH_2NH_2} + H_2O$$

$$\underset{\text{Acetone oxime}}{(CH_3)_2C{=}NOH} \xrightarrow[\text{or } LiAlH_4]{Na/C_2H_5OH} \underset{\text{Isopropylamine}}{(CH_3)_2CH\,NH_2} + H_2O$$

5. By reductive-amination of aldehydes and ketones When an aldehyde or a ketone is allowed to react with a mixture of excess of ammonia and H_2 gas at 140–150°C under high pressure of 20–150 atmospheres, in the presence of Raney Ni, a primary amine is obtained. This process which involves conversion of the carbonyl compound to the corresponding imine by treatment with NH_3 and its subsequent reduction is called *reductive-amination*.

Examples:

$$\underset{\text{Acetaldehyde}}{CH_3CHO + NH_3} \xrightarrow{-H_2O} \underset{\text{Imine}}{\left[CH_3CH{=}NH\right]} \xrightarrow{H_2/Ni} \underset{\text{Ethylamine}}{CH_3CH_2NH_2}$$

$$\underset{\text{Acetone}}{(CH_3)_2C{=}O + NH_3} \xrightarrow{-H_2O} \underset{\text{Imine}}{\left[(CH_3)_2C{=}NH\right]} \xrightarrow{H_2/Ni} \underset{\text{Isopropylamine}}{(CH_3)_2CH\,NH_2}$$

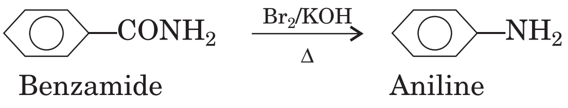
A variation of the classical reductive amination procedure uses sodium cyanoborohydride ($NaBH_3CN$) instead of H_2 as the reducing agent. For example:

$$\underset{\text{Benzaldehyde}}{PhCHO} + \underset{\text{Ethylamine}}{CH_3CH_2NH_2} \xrightarrow[\text{MeOH(solvent)}]{NaBH_3CN} \underset{N\text{-Ethylbenzylamine (90\%)}}{PhCH_2NHCH_2CH_3}$$

6. By Hofmann rearrangement or Hofmann hypobromite reaction When an acid amide is allowed to react with Br_2 in the presence of alkali at about 70°C, a primary amine with one C-atom less than the parent acid amide is obtained.

Examples:

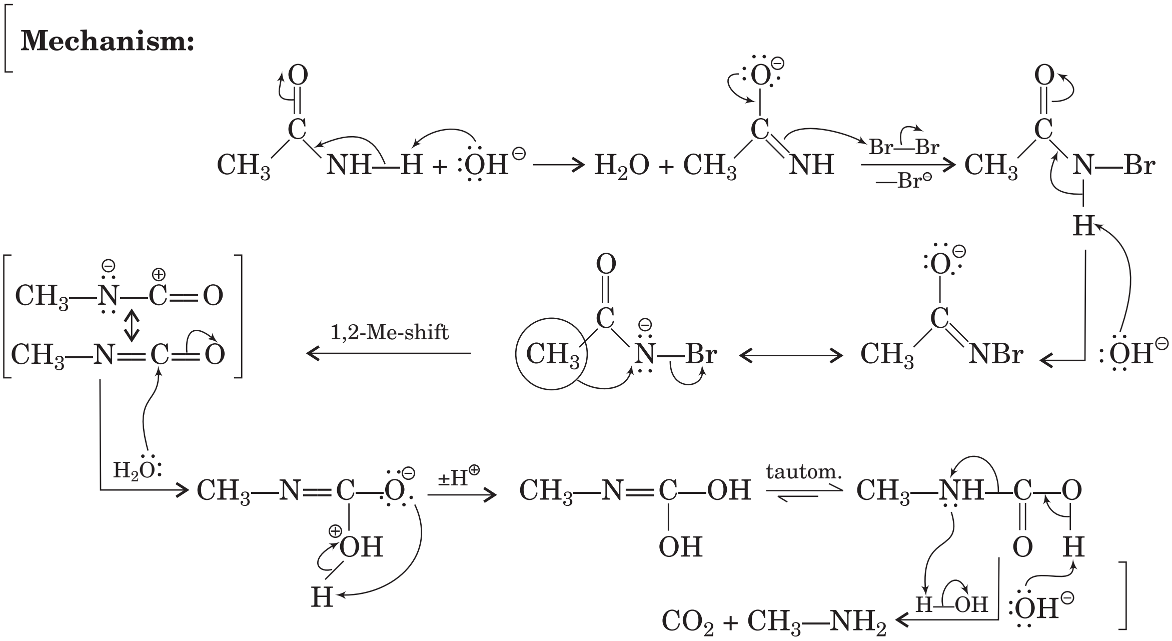
$$\underset{\text{Acetamide}}{CH_3{-}CONH_2} + Br_2 + 4KOH \xrightarrow{70°C} 2KBr + K_2CO_3 + 2H_2O + \underset{\substack{\text{Methylamine}\\ \text{(a 1° amine)}}}{CH_3NH_2}$$



Benzamide

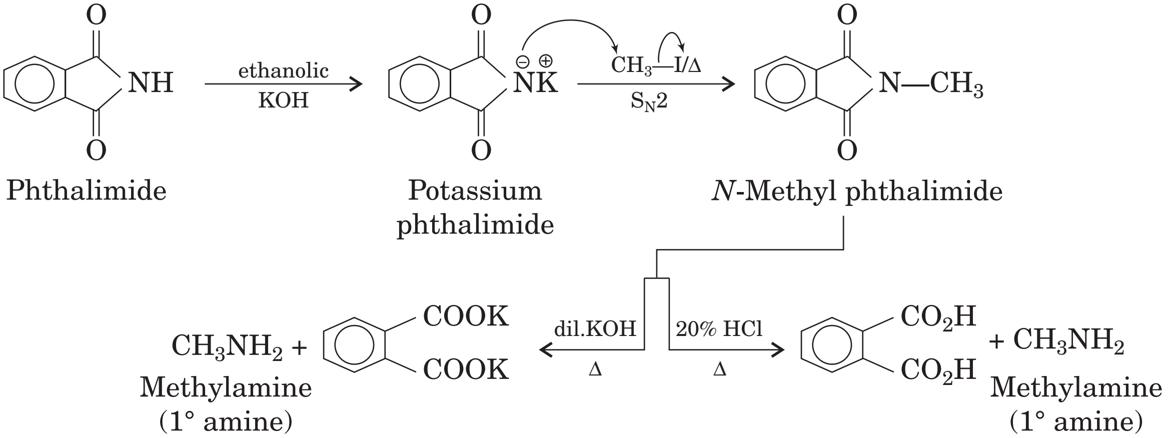
Aniline
(a 1° amine)

Mechanism:

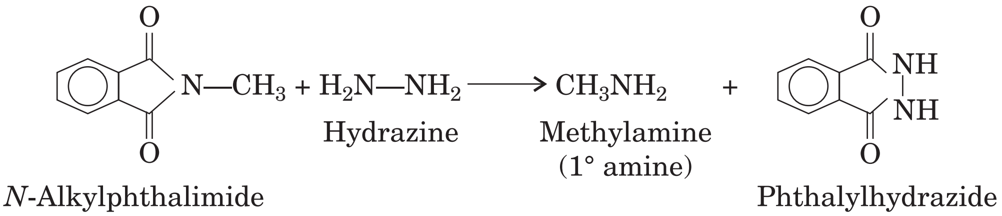


7. By Gabriel synthesis In this method phthalimide is converted, by means of ethanolic potassium hydroxide, into its salt which, on heating with an alkyl halide, gives the *N*-alkyl phthalimide. This is subsequently hydrolysed to phthalic acid and a primary amine by heating with 20% hydrochloric acid under pressure or by refluxing with KOH solution.

Example:



Primary amines can also be obtained by hydrazinolysis (cleavage by hydrazine) of *N*-alkylphthalimide. This method is more effective than acidic or alkaline hydrolysis.



Gabriel's synthesis is a very useful method since it gives a pure primary amine.

8. By Grignard synthesis Grignard reagents react with chloramine to form primary amines. It is a very effective method for preparing primary amine in which the –NH_2 group is attached to a tertiary carbon atom.

Example:

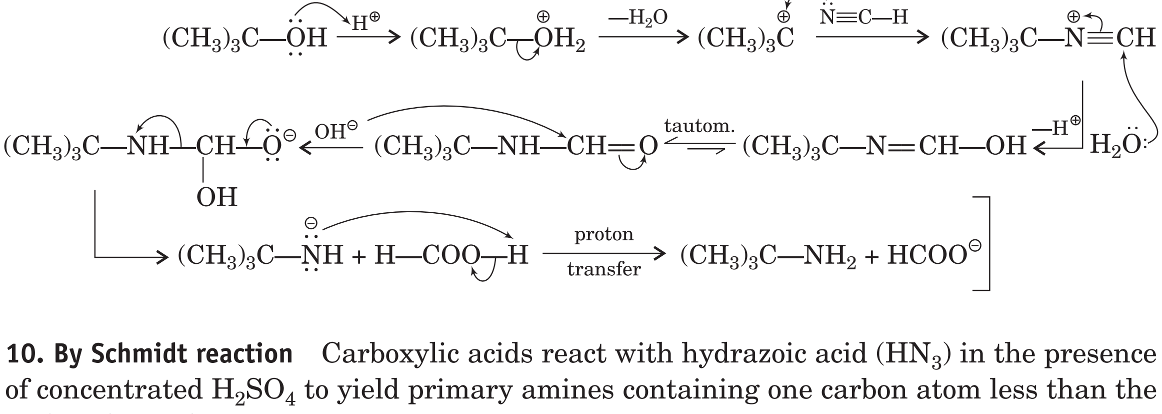
$$\underset{tert\text{-Butyl bromide}}{(CH_3)_3C{-}Br} \xrightarrow[\text{ether}]{Mg} (CH_3)_3C\;Mg\;Br \xrightarrow{Cl{-}NH_2} \underset{tert\text{-Butylamine}}{(CH_3)_3C{-}NH_2} + Mg\;BrCl$$

9. By the Ritter reaction A good method for preparing primary amines containing a *t*-alkyl group is by the *Ritter reaction*. This reaction depends on the formation of intermediate carbocations, and hence is mainly used with *t*-alcohols (or alkenes that can produce *t*-carbocations). The reaction occurs between alcohol (or alkene) and alkyl cyanide (or HCN) in the presence of sulphuric acid to produce an amide which on alkaline hydrolysis yield the primary amine.

Example:

$$(CH_3)_3COH \xrightarrow[NaCN]{H_2SO_4} (CH_3)_3CNHCHO \xrightarrow[\Delta]{OH^{\ominus}/H_2O} (CH_3)_3CNH_2 + HCO_2^{\ominus}$$

Mechanism:



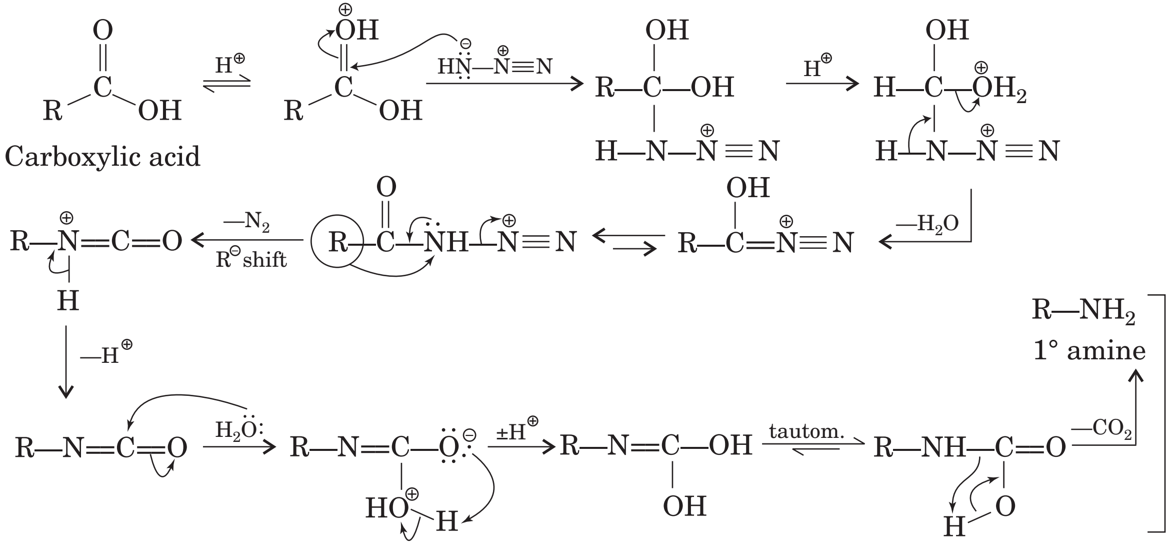
10. By Schmidt reaction Carboxylic acids react with hydrazoic acid (HN_3) in the presence of concentrated H_2SO_4 to yield primary amines containing one carbon atom less than the carboxylic acids.

Examples:

$$\underset{\text{Acetic acid}}{CH_3COOH} + HN_3 \xrightarrow{\text{conc. } H_2SO_4} \underset{\substack{\text{Methylamine}\\ \text{(a 1° amine)}}}{CH_3NH_2} + CO_2 + N_2$$

$$\underset{\text{Benzoic acid}}{C_6H_5COOH + HN_3} \xrightarrow{\text{conc. } H_2SO_4} \underset{\substack{\text{Aniline}\\ \text{(a 1° amine)}}}{C_6H_5NH_2} + CO_2 + N_2$$

Mechanism:



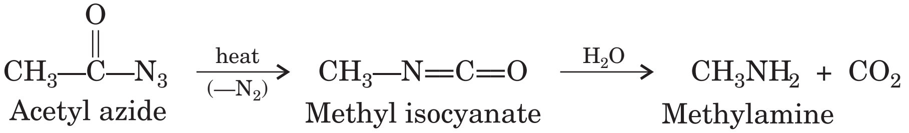
11. By hydrolysis of alkyl isocyanides At ordinary temperature, alkyl isocyanides undergo hydrolysis by dilute HCl to give primary amines.

Example:

$$CH_3{-}NC + 2H_2O \xrightarrow[\text{(hydrolysis)}]{\text{dil.HCl}} \underset{\substack{\text{Methylamine}\\ \text{(a 1° amine)}}}{CH_3{-}NH_2} + HCOOH$$

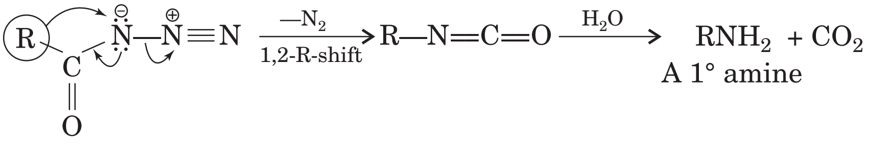
12. By Curtius rearrangement When acyl azides are heated with an inert solvent like benzene, chloroform, etc., alkyl isocyanates are obtained. These on hydrolysis yield 1° amines. The reaction is known as *Curtius reaction* or *Curtius rearrangement*.

Example:



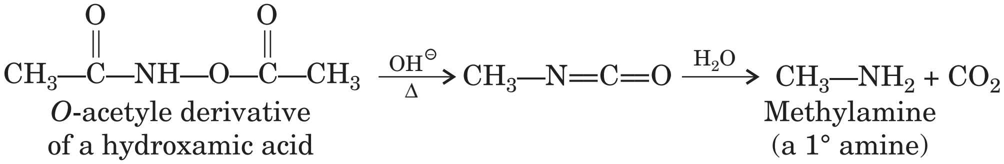
$$\underset{\text{Acetyl azide}}{CH_3-\overset{\overset{O}{\|}}{C}-N_3} \xrightarrow[(-N_2)]{\text{heat}} \underset{\text{Methyl isocyanate}}{CH_3-N=C=O} \xrightarrow{H_2O} \underset{\text{Methylamine}}{CH_3NH_2 + CO_2}$$

Mechanism:



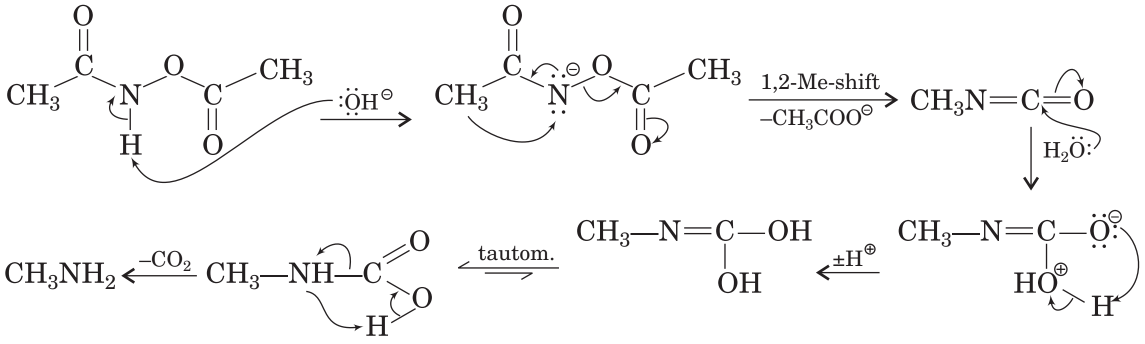
13. By Lossen rearrangement The Lossen rearrangement offers a good method for preparing pure primary amines free from secondary and tertiary amines. The *O*-acyl derivatives of hydroxamic acids RCONHOH, gives isocyanate (RNCO) when heated with bases. The isocyanates undergoes hydrolysis instantly to yield 1° amines.

Example:



$$\underset{\substack{\textit{O}\text{-acetyle derivative}\\ \text{of a hydroxamic acid}}}{CH_3-\overset{\overset{O}{\|}}{C}-NH-O-\overset{\overset{O}{\|}}{C}-CH_3} \xrightarrow[\Delta]{OH^{\ominus}} CH_3-N=C=O \xrightarrow{H_2O} \underset{\substack{\text{Methylamine}\\ \text{(a 1° amine)}}}{CH_3-NH_2 + CO_2}$$

Mechanism:



1.1.1.2 Preparation of Secondary Amines

1. By reduction of alkyl isocyanides Alkyl isocyanides (RNC) are reduced by H_2/Ni or Na/EtOH to form secondary amines.

Example:

$$\underset{\text{Ethyl isocyanide}}{C_2H_5NC} \xrightarrow[\text{or Na}/C_2H_5OH]{H_2/Ni} \underset{\text{Ethylmethylamine (a 2° amine)}}{C_2H_5NHCH_3}$$

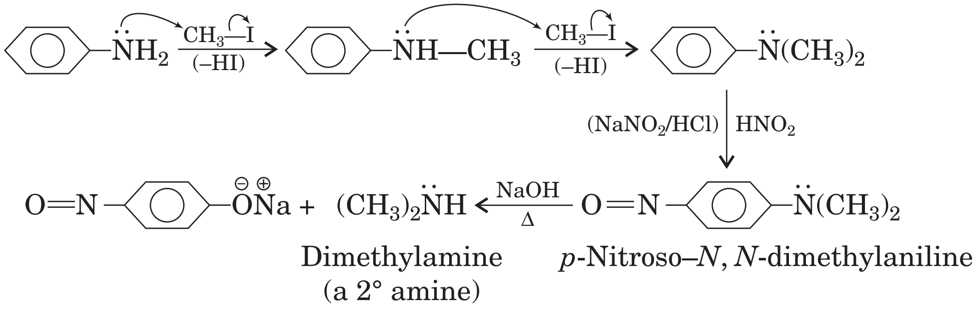
2. By alkylation of primary amines Secondary amines can be prepared by heating primary amines with requisite amount (1:1 molor ratio) of alkyl halide (preferably alkyl iodides).

Example:

$$\underset{\substack{\text{Ethylamine}\\ \text{(a 1° amine)}}}{C_2H_5NH_2} + C_2H_5I \xrightarrow{\Delta} \underset{\substack{\text{Diethylamine}\\ \text{(a 2° amine)}}}{(C_2H_5)_2NH} + HI$$

3. By using aniline and alkyl halide When aniline is heated with an alkyl halide, dialkylaniline is obtained. This on treatment with nitrous acid (i.e., $NaNO_2$/HCl) gives *p*-nitroso-*N*, *N*-dialkylamine which on alkaline hydrolysis produces a secondary amine.

Example:



4. By using calcium cyanamide Secondary amines can be prepared from calcium cyanamide by the following sequence of reactions.

$$\begin{tikzcd} \underset{\text{Calcium cyanimide}}{CaNCN} \arrow[r, "NaOH"] & Na_2NCN \arrow[r, "2CH_3I"] & (CH_3)_2NCN \arrow[d, "HCl"] \\ & & NH_3 + CO_2 + (CH_3)_2NH_2 \end{tikzcd}$$

5. By reductive alkylation of a primary amine using a carbonyl compound When a mixture of a carbonyl compound, a primary amine and hydrogen gas is passed over Ni catalyst under high pressure and high temperature, a secondary amine is obtained.

Example:

$$\underset{\text{Acetaldehyde}}{CH_3CHO} + \underset{\substack{\text{Methylamine}\\ \text{(a 1° amine)}}}{CH_3NH_2} + H_2 \xrightarrow[\substack{\text{high temperature}\\ \text{\& high pressure}}]{Ni} \underset{\substack{\text{Ethylmethylamine}\\ \text{(a 2° amine)}}}{CH_3CH_2NHCH_3}$$

1.1.1.3 Preparation of Tertiary Amines

1. By alkylation of ammonia Tertiary amines can be prepared by heating excess of alkyl halide with alcoholic solution of ammonia. It is, in fact, the best method for the preparation of 3° amines.

Example:

$$\underset{\substack{\text{Methyl}\\ \text{iodide}}}{3\,CH_3I} + NH_3 \longrightarrow \underset{\substack{\text{Trimethylamine}\\ \text{(a 3° amine)}}}{(CH_3)_3N} + 3HI$$

2. By reductive alkylation of a secondary amine using a carbonyl compound When a mixture of a carbonyl compound, a secondary amine and hydrogen gas is passed over nickel catalyst under pressure, a tertiary amine is produced.

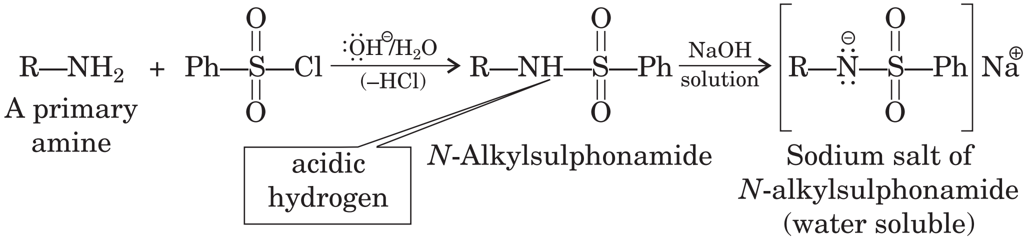
Example:

$$\underset{\text{Acetaldehyde}}{CH_3\text{—}CHO} + \underset{\substack{\text{Diethylamine}\\ \text{(a 2° amine)}}}{Et_2NH} + H_2 \xrightarrow[\text{Pressure}]{\text{Ni}} \underset{\substack{\text{Triethylamine}\\ \text{(a 3° amine)}}}{Et_3N} + H_2O$$

1.1.2 Distinction between Primary, Secondary and Tertiary Amines

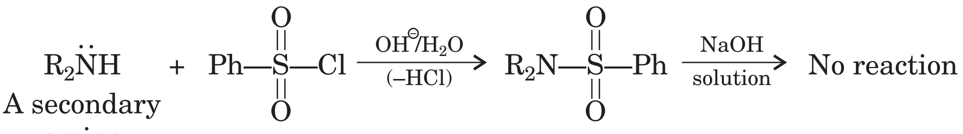
1. Hinsberg test The reactions of amines with benzene sulphonyl chloride ($PhSO_2Cl$) form the basis of the classical *Hinsberg test* to determine the class of an amine. In this test, the given amine is treated with benzene sulphonyl chloride (Hinsberg reagent) in the presence of cold aqueous NaOH.

(a) A primary amine produces *N*-alkylsulphonamide which contains an acidic hydrogen and hence dissolves in NaOH solution to form the soluble sodium salt. The benzene sulphonyl group is strongly electron-attracting, and thereby facilitates the release of the proton attached to the N atom.



$$\underset{\substack{\text{A primary}\\ \text{amine}}}{R\text{—}NH_2} + Ph\text{—}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}\text{—}Cl \xrightarrow[(-HCl)]{:\ddot{O}H^{\ominus}/H_2O} \underset{N\text{-Alkylsulphonamide}}{R\text{—}NH\text{—}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}\text{—}Ph} \xrightarrow[\text{solution}]{\text{NaOH}} \underset{\substack{\text{Sodium salt of}\\ N\text{-alkylsulphonamide}\\ \text{(water soluble)}}}{\left[R\text{—}\overset{\ominus}{\ddot{N}}\text{—}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}\text{—}Ph\right]Na^{\oplus}}$$

(b) A secondary amine produces *N*, *N*-dialkylsulphonamide which, containing no acidic hydrogen, precipitates immediately as it is incapable of forming sodium salt with sodium hydroxide.



$$R_2\ddot{N}H + Ph-\overset{\overset{O}{||}}{\underset{\underset{O}{||}}{S}}-Cl \xrightarrow[(-HCl)]{OH^{\ominus}/H_2O} R_2N-\overset{\overset{O}{||}}{\underset{\underset{O}{||}}{S}}-Ph \xrightarrow[\text{solution}]{NaOH} \text{No reaction}$$

A secondary amine

N,*N*-Dialkylsulphonamide (insoluble precipitate)

(c) A tertiary amine with no available hydrogen does not react with $PhSO_2Cl$ and remain as insoluble material.

$$R_3N + PhSO_2Cl \xrightarrow{OH^{\ominus}/H_2O} \text{No reaction}$$

A tertiary amine

The limitation of this test is that the amines must be water-insoluble liquids.

[It is to be noted that benzene sulphonyl chloride, $PhSO_2Cl$, was used originally, but has now been replaced by *p*-toluenesulphonyl chloride, *p*-$CH_3C_6H_4SO_2Cl$.]

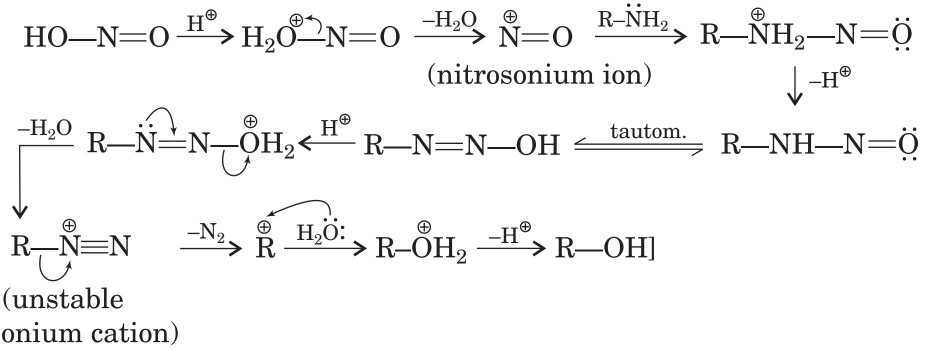
2. Behaviour towards nitrous acid Primary, secondary and tertiary amines give characteristic reactions with nitrous acid and the observations of these reactions help to distinguish among them.

(a) Primary amines react with HNO_2 to form primary alcohol and nitrogen gas.

$$RNH_2 + HNO_2 \xrightarrow{(NaNO_2/HCl)} ROH + N_2 + H_2O$$

A primary amine

[Mechanism:



$$HO-N=O \xrightarrow{H^{\oplus}} H_2\overset{\oplus}{O}-N=O \xrightarrow{-H_2O} \overset{\oplus}{N}=O \xrightarrow{R-\ddot{N}H_2} R-\overset{\oplus}{N}H_2-N=\ddot{O} \xrightarrow{-H^{\oplus}} R-NH-N=\ddot{O} \rightleftharpoons_{\text{tautom.}} R-N=N-OH \xrightarrow{H^{\oplus}} R-\ddot{N}=N-\overset{\oplus}{O}H_2 \xrightarrow{-H_2O} R-\overset{\oplus}{N}\equiv N \xrightarrow{-N_2} \overset{\oplus}{R} \xrightarrow{H_2\ddot{O}:} R-\overset{\oplus}{O}H_2 \xrightarrow{-H^{\oplus}} R-OH]$$

(b) Secondary amines react with nitrous acid to form nitrosamines which are oily liquids. Nitrogen gas is not evolved in this reaction.

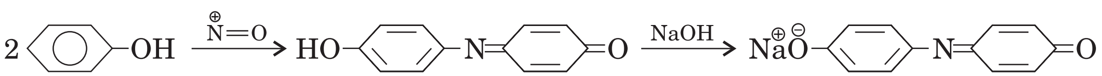
$$R_2NH \xrightarrow[(NaNO_2/HCl)]{HNO_2} R_2N-N=O$$

A 2° amine

N-Nitrosamine (yellow oil)

Liberman's nitrosamine reaction It is used as a test for 2° amines. Nitrosamine form red solution when heated with a few drops of phenol and conc. H_2SO_4. The red solution turns blue when NaOH solution is added to it. This colour reaction is known as Liberman's nitrosamine reaction. Sulphuric acid liberates nitrous acid from nitrosamines and this reacts with phenol to form *p*-nitrosophenol which then combines with another molecule of phenol to give red-coloured indophenol. In alkaline solution, indophenol anion is formed which is blue in colour.

$$R_2N{-}N{=}O \xrightarrow{H_2SO_4} R_2NH + HNO_2;\ HNO_2 + H_2SO_4 \rightarrow \overset{\oplus}{N}O + HSO_4^{\ominus} + H_2O$$



Indophenol
(red)

Indophenol salt
(blue)

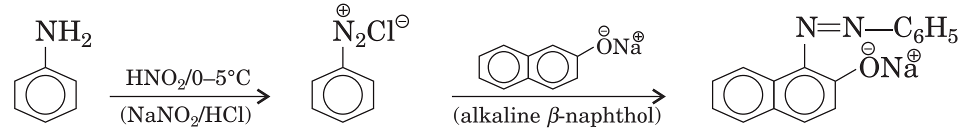
(c) Tertiary amines dissolve in cold nitrous acid to form nitrite salts.

$$R_3N + HNO_2 \longrightarrow \underset{\text{(Salt)}}{R_3\overset{\oplus}{N}HNO_2^{\ominus}}$$

Therefore, the three classes of amines can be distinguished from their reaction with nitrous acid.

Primary, secondary and tertiary aromatic amines also give characteristic reactions with nitrous acid:

(a) Primary aromatic amines Aniline, for example, reacts with HNO_2 ($NaNO_2$ + HCl) at 0–5°C to form benzene-diazonium chloride. When a few drops of this solution is added to an excess of cold alkaline solution of *β*-naphthol, a red dye is obtained.

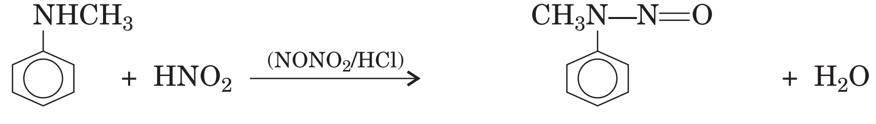


Aniline
(a 1° amine)

Benzenediazonium
chloride

1-Phenylazo-2-
naphthol (sodium salt)
(red ozo-dye)

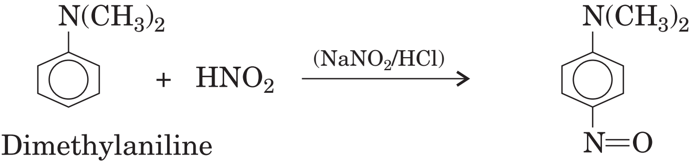
(b) Secondary aromatic amines Monomethylaniline, for example, reacts with a cold solution of HNO_2 (i.e., $NaNO_2$ + HCl) to form *N*-nitrosoamine which is a light yellow liquid, insoluble in water.



N-Methylaniline
(a 2° amine)

N-Nitroso-*N*-methylaniline
(a light yellow liquid)

(c) Tertiary aromatic amines *N*, *N*-Dimethylaniline, for example, reacts with nitrous acid (i.e., $NaNO_2$ + HCl) to form *p*-nitroso-*N*, *N*-dimethylaniline which is a green solid.



N, *N*-Dimethylaniline
(a 3° amine)

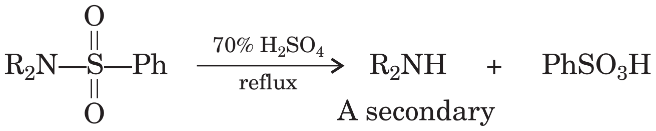
p-Nitroso-*N*, *N*-dimethylaniline
(a green solid)

Due to lack of hydrogen on nitrogen, nitrosation (an electrophilic aromatic substitution) occurs to yield a nitroso derivative.

1.1.3 Separation of Primary, Secondary and Tertiary Amines by Hinsberg's Method

When an excess of benzene sulphonyl chloride and alkali are added to a mixture of 1°, 2° and 3° amines, the 3° amine remains unreached. It is separated from the sulphonamide mixture by distillation or by solvent extraction.

Between the sulphonamides of 1° and 2° amines the first one remain dissolved in alkali and the second one is then filtered off. *N*, *N*-dialkylsulphonamide gives back the secondary amine when distilled with 70% H_2SO_4 or 25% HCl.

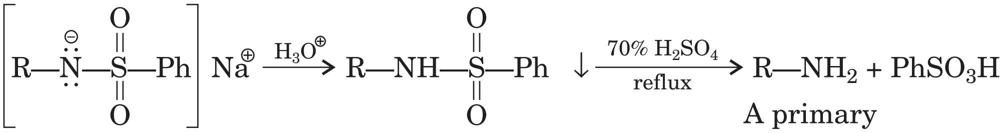


$$R_2N-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-Ph \xrightarrow[\text{reflux}]{70\%\ H_2SO_4} R_2NH + PhSO_3H$$

N, *N*-Dialkylbenzene sulphonamide

A secondary amine

The alkaline solution (filtrate) is then acidified to precipitate *N*-alkylbenzenesulphonamide of 1° amine and then the precipitate is distilled with 70% H_2SO_4 or 25% HCl to get back the primary amine.



$$\left[R-\overset{\ominus}{\underset{\cdot\cdot}{\ddot{N}}}-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-Ph\right]\overset{\oplus}{Na} \xrightarrow{H_3O^{\oplus}} R-NH-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O}{\|}}{S}}-Ph\downarrow \xrightarrow[\text{reflux}]{70\%\ H_2SO_4} R-NH_2 + PhSO_3H$$

N-Alkylbenzenesulphonamide

A primary amine

1.1.4 Reactions

1. Eschweiler–Clarke methylation Primary and secondary amines form *N*-methyl derivatives when heated to 100°C with a mixture of formaldehyde and formic acid. One H-atom of

$–NH_2$ or $\rangle NH$ group is replaced by $–CH_3$ group. This is what is called *Eschweiler–Clarke methylation*.

Examples:

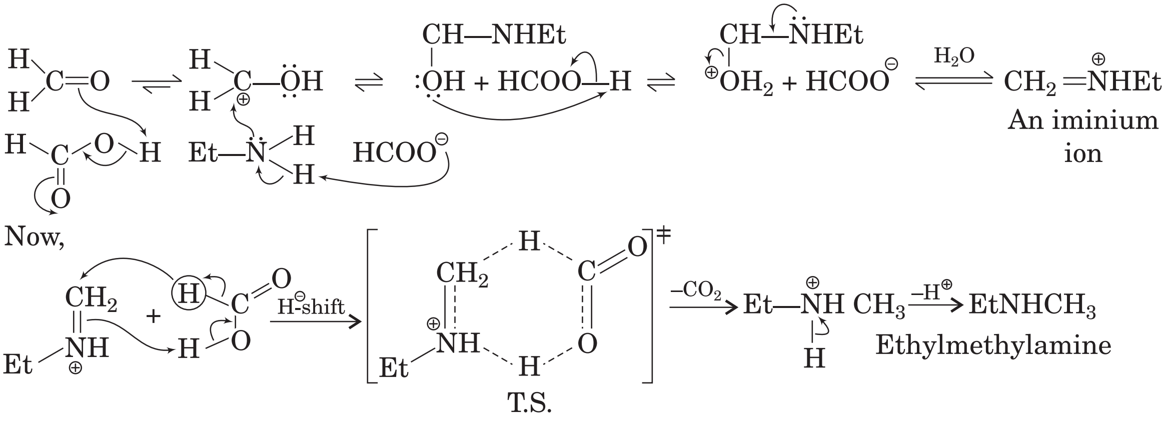
$$CH_3CH_2NH_2 + HCHO + HCOOH \longrightarrow CH_3CH_2NHCH_3 + CO_2 + H_2O$$

Ethylamine → Ethylmethylamine

$$(CH_3)_2NH + HCHO + HCOOH \longrightarrow (CH_3)N + CO_2 + H_2O$$

Dimethylamine → Triethylamine

Mechanism: The mechanism of the reaction involves the steps as follows:



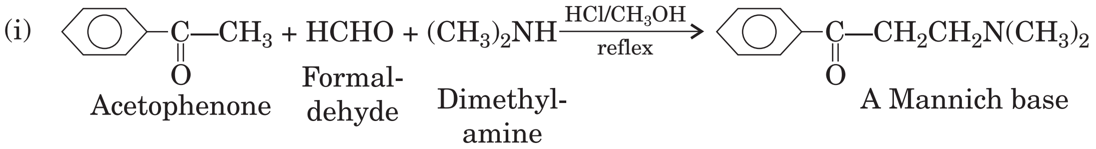
Formic acid acts as a reducing agent by transferring a hydride ion to the electron-deficient carbon and is oxidized to CO_2.

2. Mannich reaction The condensation of an enolizable carbonyl compound (an aldehyde or a ketone) with formaldehyde and ammonia or a primary or secondary amine to form its aminomethyl or substituted aminomethyl derivative (called a *Mannich base*) is known as the *Mannich reaction*.

The reaction is usually carried out in acid solution (but may also be base-catalyzed). The commonly used solvents are water, methanol, and ethanol. Usually, secondary amines (e.g., dimethylamine, diethylamine, piperidine, etc.) are used to avoid side reactions.

Examples:

(i)

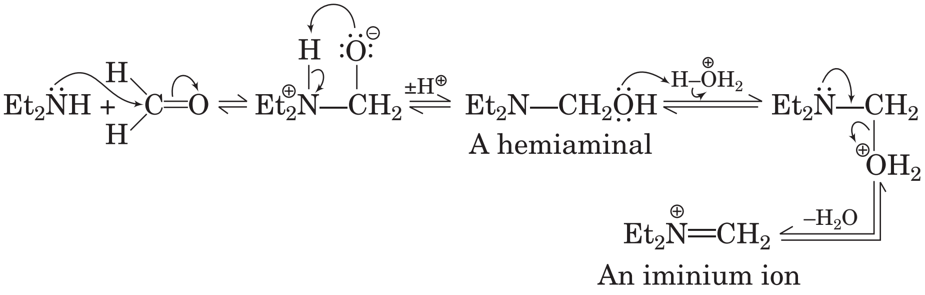


(ii) $CH_3COCH_3 + HCHO + (C_2H_5)_2\ NH \xrightarrow[\text{reflex}]{HCl/CH_3OH} CH_3CO(CH_2)_2N(C_2H_5)_2$

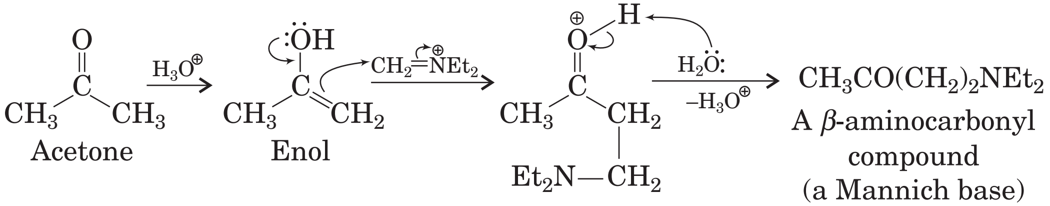
Acetone   Formal-dehyde   Dimethyl-amine   A Mannich base

Mechanism of the reaction: The mechanism of the reaction involves the steps as follows:

Step 1: Formaldehyde reacts with ethylamine ($C_2H_5NH_2$) to form an iminium ion through the formation of a hemiaminal.



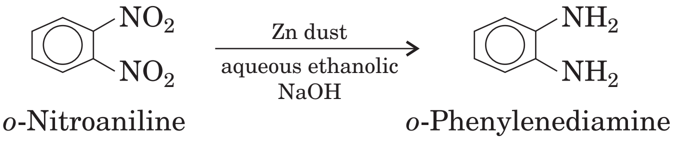
Step 2: The enol form of the active hydrogen compound reacts with the iminium cation to form a β-aminocarbonyl compound (a Mannich base).



1.1.5 Phenylenediamines

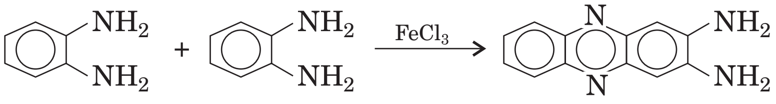
1.1.5.1 o-Phenylenediamine (benzene-1,2-diamine or 1,2-diaminobenzene)

1. Preparation It is best prepared by reducing *o*-nitroaniline with zinc dust and aqueous ethanolic sodium hydroxide (74–85%).

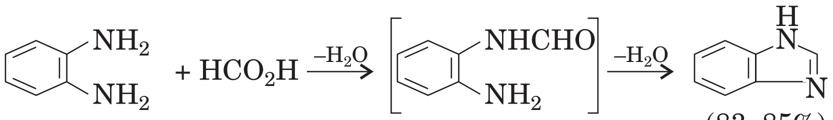


2. Reactions The most characteristic property of *o*-diamines is the ease with which they form heterocyclic compounds.

(i) When *o*-phenylenediamine is treated with ferric chloride solution, a dark red colour is produced due to the formation of 2,3-diaminophenazine.

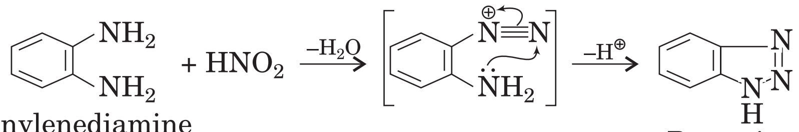


(ii) Benzimidazoles are obtained when *o*-phenylenediamine is heated with organic acids. For example:



o-Phenylenediamine (83–85%)

(iii) When *o*-phenylenediamine is treated with nitrous acid (a solution of the diaminocompound in acetic acid is treated with an aqueous solution of sodium nitrite), benztriazole is formed.

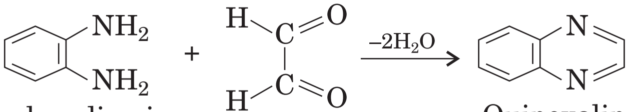


o-Phenylenediamine

Benztriazole

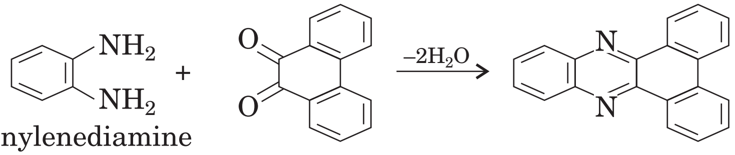
(75–81%)

(iv) *o*-Phenylenediamine condenses with *α*-dicarbonyl compounds to form quinoxalines. For example:



o-Phenylenediamine Glyoxal Quinoxaline

This reaction is used to identify *o*-diamines. The *α*-dicarbonyl compound used for this purpose is phenanthraquinone and this results in formation of a sparingly soluble phenazine derivative.

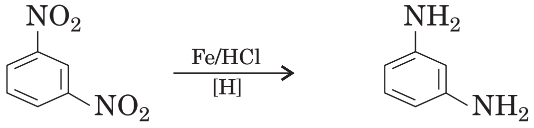


o-Phenylenediamine

Phenanthraquinone A phenazine derivative

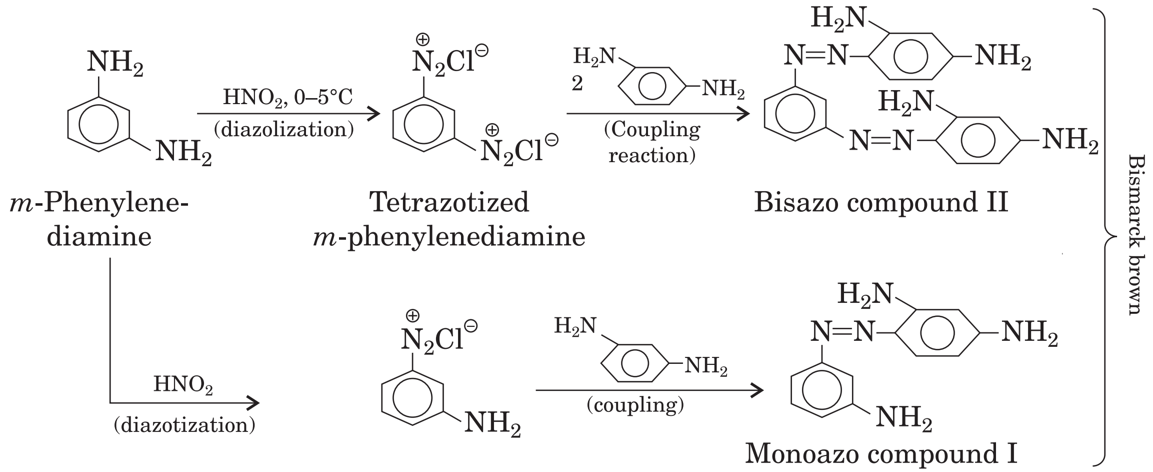
1.1.5.2 m-Phenylenediamine (benzene-1,3-diamine or 1,3-diamobenzene)

1. Preparation It is best prepared by the reduction of *m*-dinitrobenzene with iron and hydrochloric acid.



m-Dinitrobenzene *m*-Phenylenediamine

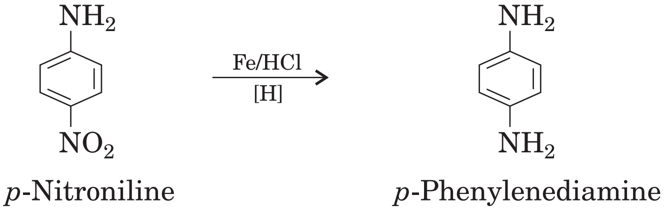
2. Reactions Its must characteristic reaction is the formation of a brown dye known as Bismarck brown. This is, in fact, a mixture of two compounds, I and II. This mixture is obtained by the action of HNO_2 on *m*-phenylenediamine.

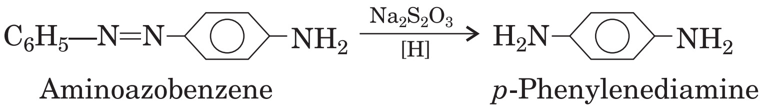


This reaction is used as a colorimetric method for determination of nitrites in water; a yellow colour is produced even when nitrites are present in traces.

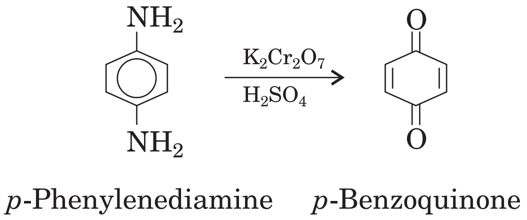
1.1.5.3 p-Phenylenediamine (benzene-1,4-diamine or 1,4-diaminobenzene)

1. Preparation It may be prepared by the reduction of *p*-nitroaniline or aminoazobenzene.





2. Reactions On vigorous oxidation it forms *p*-benzoquinone.



p-Phenylenediamine can be diazotized in the usual way and is used in the synthesis of dyes.

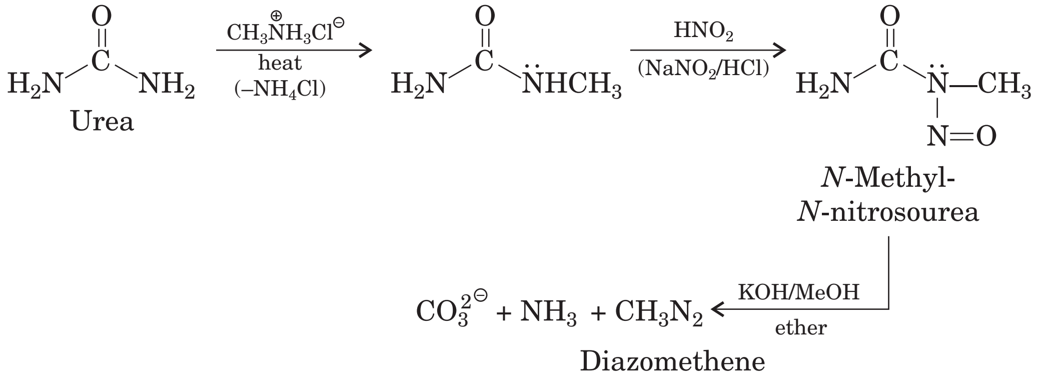
1.2 DIAZOMETHANE (CH_2N_2)

1.2.1 Preparation of Diazomethane

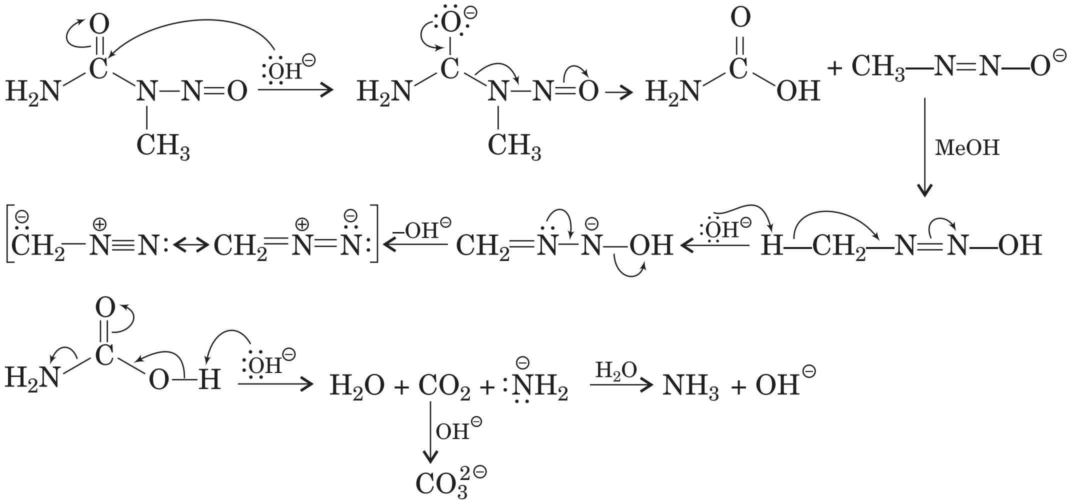
Diazomethane can be prepared by the following methods:

(a) Method of von Pechmann

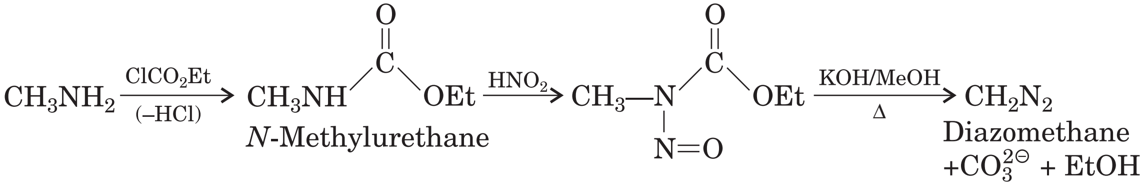
(i) *From N-methyl-N-nitrosourea:*



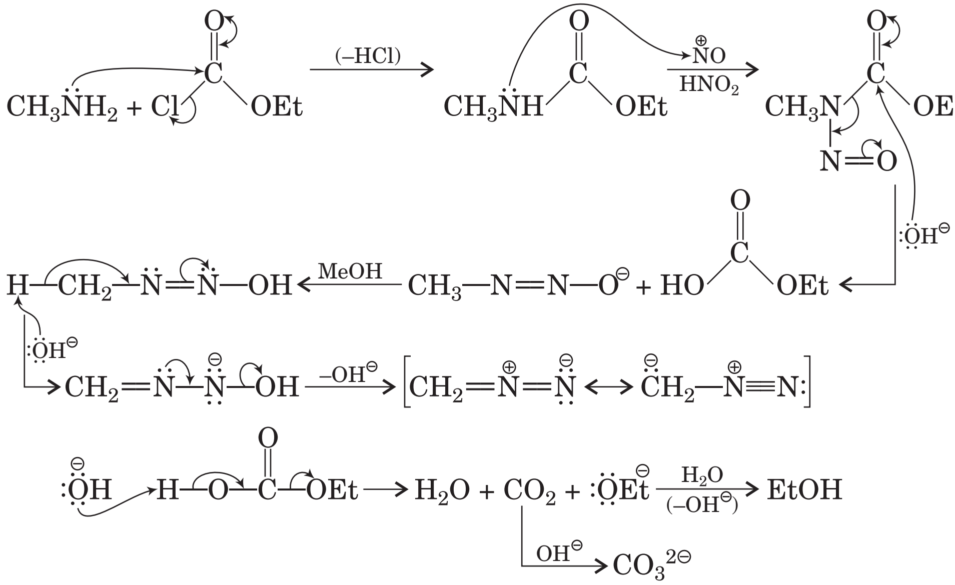
Mechanism of the final step:



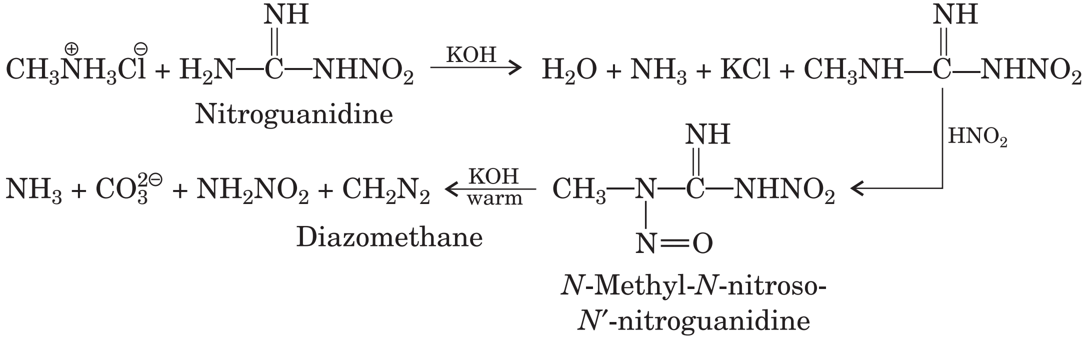
(ii) *From N-methylurethane:*



Mechanism of the reaction:



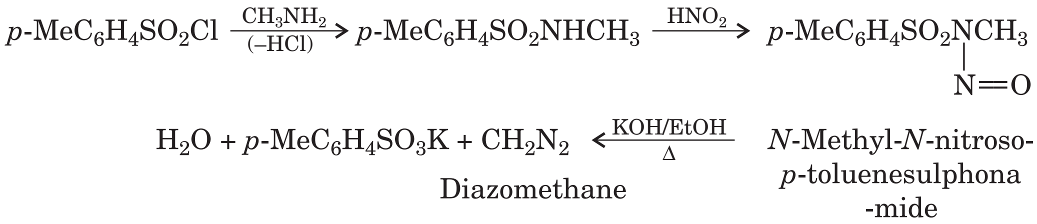
(b) Method of McKay *From N-methyl-N-nitroso-N′-nitroguanidine*



$$\overset{\oplus}{CH_3NH_3}\overset{\ominus}{Cl} + H_2N-\overset{\overset{NH}{\|}}{C}-NHNO_2 \xrightarrow{KOH} H_2O + NH_3 + KCl + CH_3NH-\overset{\overset{NH}{\|}}{C}-NHNO_2$$

$$NH_3 + CO_3^{2\ominus} + NH_2NO_2 + CH_2N_2 \xleftarrow[\text{warm}]{KOH} CH_3-\underset{\underset{N=O}{|}}{N}-\overset{\overset{NH}{\|}}{C}-NHNO_2$$

(c) Method of Backer *From N-methyl-N-nitroso-p-toluenesulphonamide:*

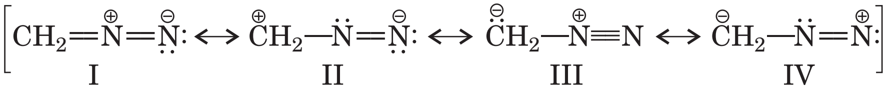


$$p\text{-}MeC_6H_4SO_2Cl \xrightarrow[(-HCl)]{CH_3NH_2} p\text{-}MeC_6H_4SO_2NHCH_3 \xrightarrow{HNO_2} p\text{-}MeC_6H_4SO_2\underset{\underset{N=O}{|}}{N}CH_3$$

$$H_2O + p\text{-}MeC_6H_4SO_3K + CH_2N_2 \xleftarrow[\Delta]{KOH/EtOH} N\text{-Methyl-}N\text{-nitroso-}p\text{-toluenesulphonamide}$$

1.2.2 Properties and Structure of Diazomethane

At room temperature, diazomethane is a gas. It is a toxic substance and should be handled carefully. The structure of diazomethane is best represented as a resonance hybrid of the following resonance structures:

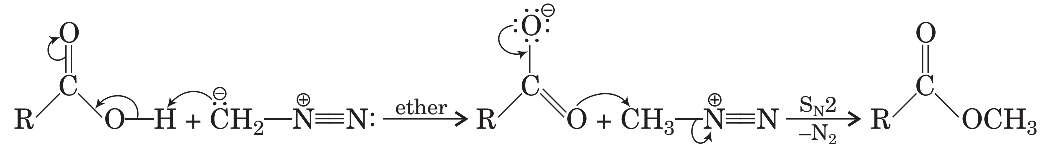


$$\left[\underset{\text{I}}{CH_2{=}\overset{\oplus}{N}{=}\overset{\ominus}{\ddot{N}}:} \longleftrightarrow \underset{\text{II}}{\overset{\oplus}{C}H_2{-}\ddot{N}{=}\overset{\ominus}{\ddot{N}}:} \longleftrightarrow \underset{\text{III}}{\overset{\ominus}{\ddot{C}}H_2{-}\overset{\oplus}{N}{\equiv}N} \longleftrightarrow \underset{\text{IV}}{\overset{\ominus}{\ddot{C}}H_2{-}\ddot{N}{=}\overset{\oplus}{N}:}\right]$$

Stability order of the canonicals: I > III > II > IV

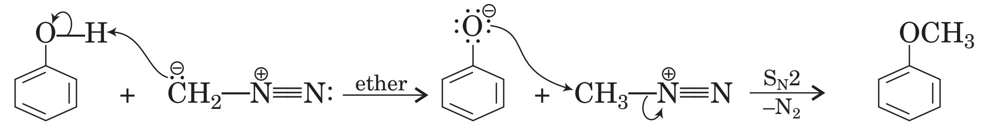
1.2.3 Uses of Diazomethane

1. Diazomethane can be used to prepare methyl esters from carboxylic acids and methyl ethers from phenols.
   The reactions take place as follows:



A carboxylic acid

A methyl ester

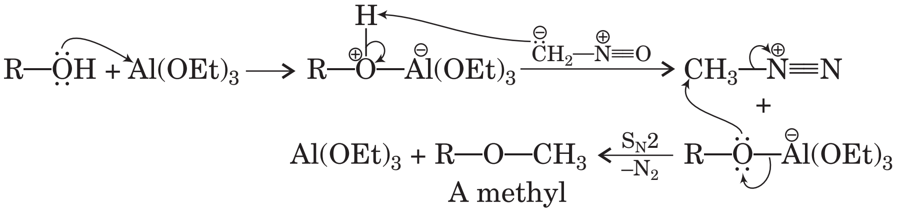


Phenol

Anisole (a methyl ether)

It is to be noted that methylation by diazomethane requires an acidic proton. Alcohols cannot be directly methylated to get the corresponding methyl ethers due to non-acidic character of the hydroxyl hydrogen. However, alcohols can be methylated in the presence of Lewis acids like aluminium alkoxides.

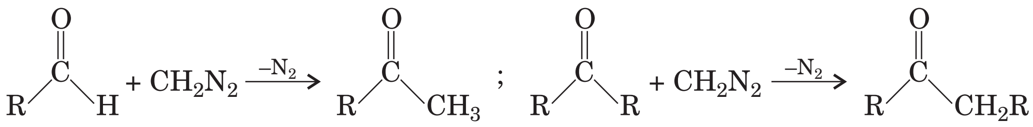
Mechanism:



A methyl ether

Fluoroboric acid (HBF_4) is a very good catalyst for primary alcohols.

2. Aldehydes can be converted to methyl ketones and ketones can be converted to their higher homologues by using diazomethane.



An aldehyde

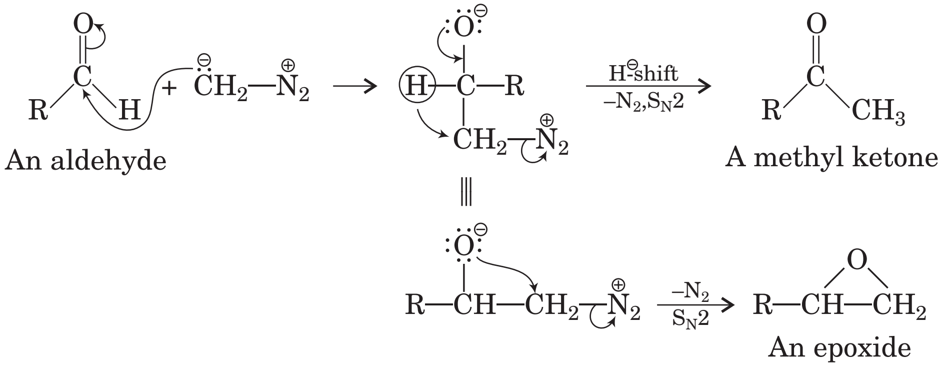
A methyl ketone

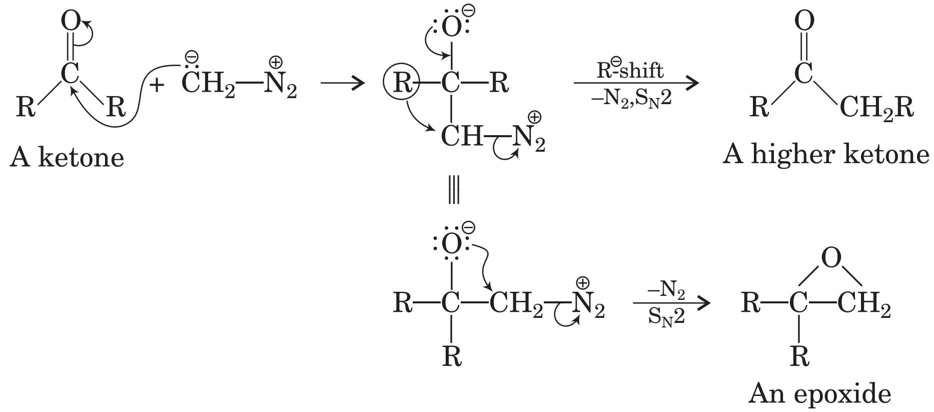
A ketone

A higher ketone

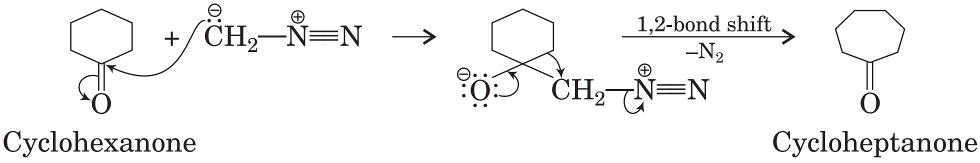
In both the cases, an epoxide is formed as the side product.

Mechanisms of the reactions:

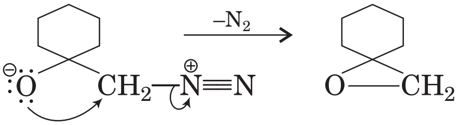




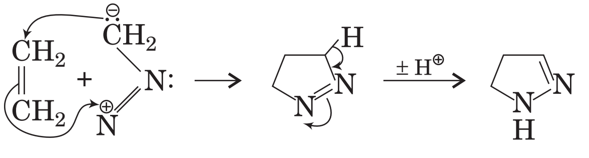
3. Ring expansion can be effected by using diazomethane. Cyclohexanone, for example, can be converted into cycloheptanone.



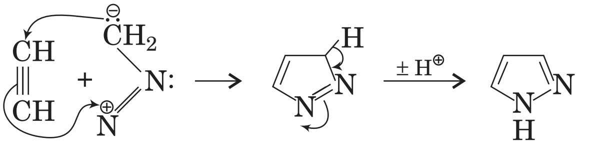
An epoxide is also formed as the side product.



4. Synthesis of nitrogen containing heterocycles: Diazomethane reacts with alkenes and alkynes as a 1,3-dipolar compound to form pyrazoline and pyrazole derivatives, respectively. Pyrazoline is formed with ethylene and pyrazole is formed with acetylene.

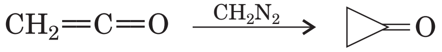


Ethylene Pyrazoline



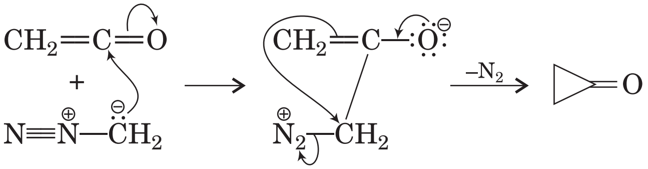
Acetylene Pyrazole

5. Cyclopropanone can be prepared by allowing ketene to react with diazomethane.

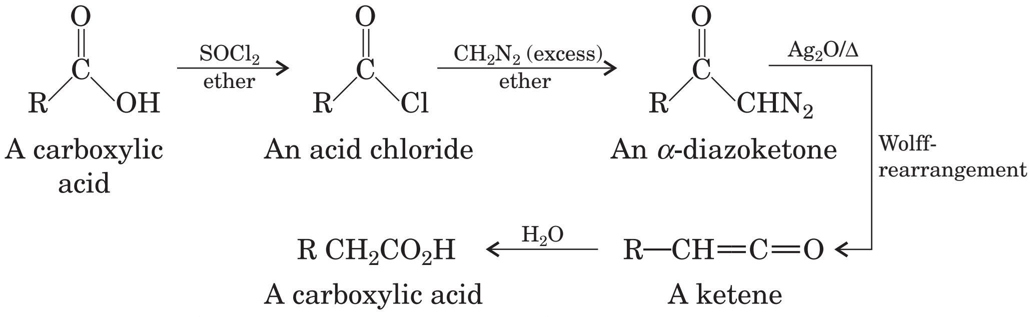


Ketene Cyclopropanone

Mechanism of the reaction:


$CH_2=C=O$
+
$N\equiv\overset{\oplus}{N}-\overset{\ominus}{C}H_2$
$CH_2=C-O^{\ominus}$
$\overset{\oplus}{N_2}-CH_2$
$-N_2$
O

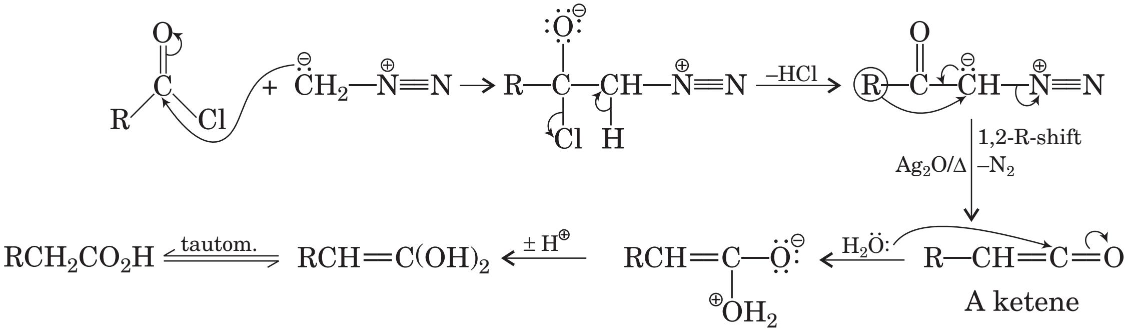
6. **Wolff rearrangement and Arndt–Eistert synthesis**
When an acyl chloride is allowed to react with excess (two molar equivalents) of diazomethane, a diazoketone is formed. This undergoes an intramolecular rearrangement, called the Wolff rearrangement, when heated with silver oxide to produce a less stable compound ketene. The ketene on hydrolysis gives the next higher acid. The conversion of an acyl chloride into its next higher carboxylic acid is known as the *Arndt–Eistert synthesis*. Since the acyl halide can easily be prepared from a carboxylic acid, therefore, a carboxylic acid (RCOOH) can easily be converted into its next higher homologue (RCH_2CO_2H). The overall process starting with the original acid is as follows:



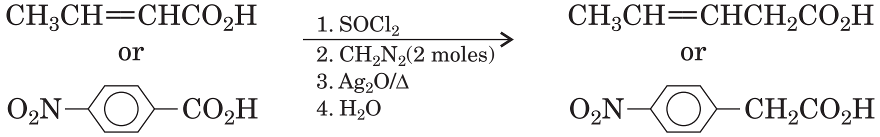
A carboxylic acid An acid chloride An α-diazoketone

A carboxylic acid (the next higher homologue) A ketene

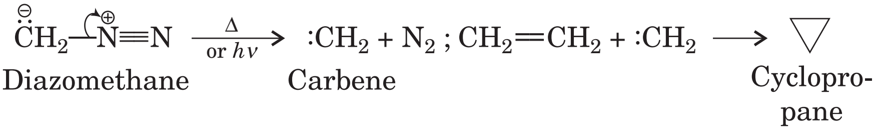
Mechanism of the Arndt–Eistert synthesis (step 2 to step 4):



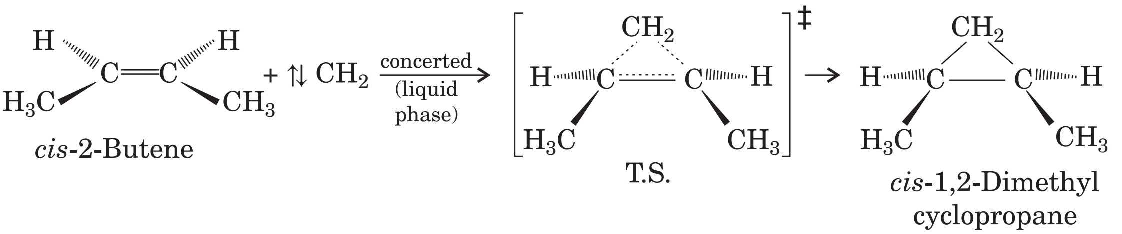
Arndt–Eistert synthesis is applicable to a wide variety of compounds and can also be applied to compounds containing unsaturations. For example:

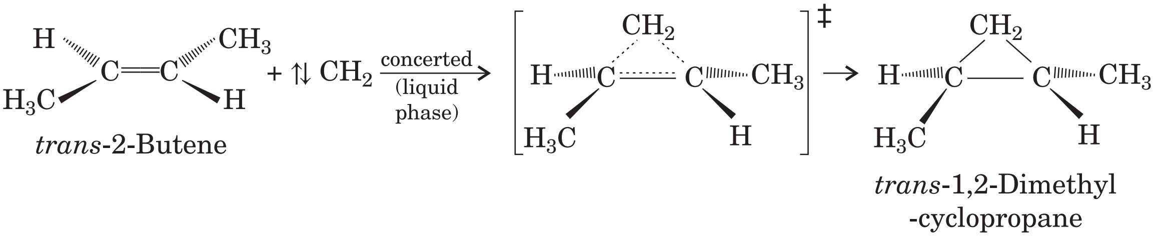


7. Diazomethane can be used to prepare cyclopropane and its derivatives. Thermolysis or photolysis of diazomethane produces methylene (carbene). It reacts with alkenes to form cyclopropane ring systems.



When photolysis of diazomethane is carried out in the presence of liquid *cis*- or *trans*-2-butene, the initially formed singlet methylene (which gets no chance to be converted into the relatively more stable triplet methylene) reacts stereospecifically to form *cis*- or *trans*-1, 2-dimethylcyclopropane.





1.3 DIAZOACETIC ESTER ($N\equiv\overset{\oplus}{N}—\overset{\ominus}{C}H—CO_2Et$)

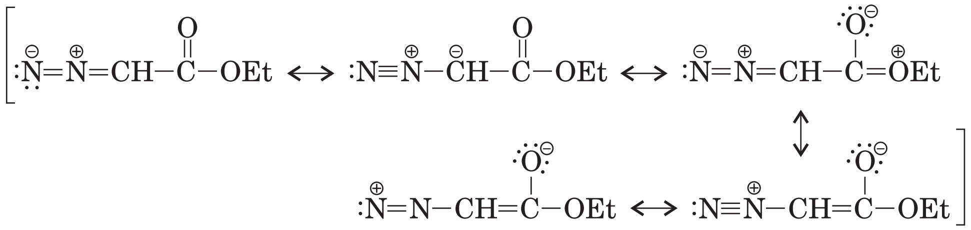
1.3.1 Preparation of Diazoacetic Ester

Diazoacetic ester or ethyl diazoacetate is also a stable compound containing $—\overset{\oplus}{N}\equiv N$ group. It can be prepared by diazotisation of a cold solution of the hydrochloride salt of ethyl glycine ester with cold solution of sodium nitrile.

$$\underset{\substack{\text{Hydrochloride salt}\\ \text{of ethyl glycine}\\ \text{ester}}}{H_2NCH_2CO_2C_2H_5 \cdot HCl} \xrightarrow[0–5°C]{NaNO_2} \underset{\substack{\text{Diazoacetic ester}\\ \text{or Ethyl diazoacetate (85\%)}}}{N\equiv\overset{\oplus}{N}-\overset{\ominus}{\ddot{C}}HCO_2C_2H_5} \quad + \quad NaCl + H_2O$$

1.3.2 Structure and Properties

The stability of diazoacetic ester may be attributed to extended resonance. Five resonance structures can be drawn for this compound.



$$\left[:\overset{\ominus}{\underset{..}{N}}=\overset{\oplus}{N}=CH-\overset{\overset{\displaystyle O}{\|}}{C}-OEt \longleftrightarrow :N\equiv\overset{\oplus}{N}-\overset{\ominus}{C}H-\overset{\overset{\displaystyle O}{\|}}{C}-OEt \longleftrightarrow :\overset{\ominus}{N}=\overset{\oplus}{N}=CH-\overset{\overset{\displaystyle \cdot\ddot{O}\cdot^{\ominus}}{|}}{C}=\overset{\oplus}{O}Et \right.$$

$$\updownarrow$$

$$\left. :\overset{\oplus}{N}=N-CH=\overset{\overset{\displaystyle \cdot\ddot{O}\cdot^{\ominus}}{|}}{C}-OEt \longleftrightarrow :N\equiv\overset{\oplus}{N}-CH=\overset{\overset{\displaystyle \cdot\ddot{O}\cdot^{\ominus}}{|}}{C}-OEt\right]$$

Because of extended resonance, diazoacetic ester is more resonance stabilized compared to diazomethane (containing only four canonical forms). At room temperature, diazoacetic ester is a liquid.

1.3.3 Uses of Diazoacetic Ester

1. Diazoacetic ester can be used to prepare glycolic ester. When boiled with dilute halogen acid, it eliminates nitrogen to form glycolic ester.

$$N_2CHCO_2Et + H_2O \xrightarrow{HCl} HOCH_2CO_2C_2H_5 + N_2$$

When, however, diazoacetic ester is warmed with *concentrated* halogen acid, ethyl halogenoacetate is formed. For example:

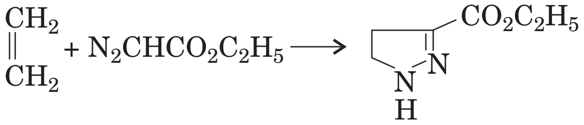
$$N_2CHCO_2C_2H_5 + HCl \longrightarrow ClCH_2CO_2C_2H_5 + N_2$$

2. Diazoacetic ester reacts with compounds containing an active hydrogen. For example, it forms acetyl glycolic ester with acetic acid, and the ethyl ether of glycolic ester with ethanol.

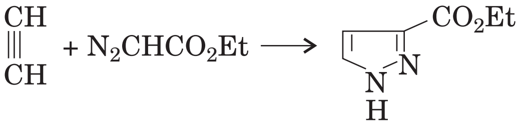
$$CH_3CO_2H + N_2CHCO_2Et \longrightarrow \underset{\text{Acetyl glycolic ester}}{CH_3COOCH_2CO_2Et} + N_2$$

$$C_2H_5OH + N_2CHCO_2Et \longrightarrow \underset{\text{Ethyl ether of glycolic ester}}{C_2H_5OCH_2COOC_2H_5} + N_2$$

3. Synthesis of nitrogen containing heterocycles: Pyrazoline derivatives can be prepared by allowing diazoacetic ester to react with ethylenic compounds. For example, it reacts with ethylene to form pyrazoline-3-carboxylic ester.



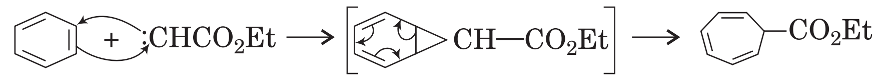
With acetylenic compounds, it forms pyrazole derivatives, e.g., with acetylene, it gives pyrazole-3-carboxylic ester.



4. When diazoacetic ester is allowed to decompose in the presence of benzene, cycloheptatrienecarboxylic ester is produced. Diazoacetic ester generates carbethoxymethylene (a carbene) when subjected to photolysis or pyrolysis.

$$\overset{\oplus}{N_2}—\overset{\ominus}{C}HCO_2Et \xrightarrow{h\nu \text{ or } \Delta} :CHCO_2Et + N_2$$

This carbene then adds to benzene to form cycloheptatrienecarboxylic ester.



Benzene Carbethoxy -methylene

Cycloheptatriene- carboxylic ester

SOLVED PROBLEMS

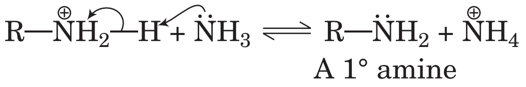
1. **Write down the reaction involved in the preparation of a primary amine from an alkyl halide or tosylate and NH_3. Mention the side reactions for which the method is not useful synthetically. How can the yield of the 1° amine (RNH_2) be increased?**

Solution

$$\ddot{N}H_3 + R—I \xrightarrow{S_N2} R—\overset{\oplus}{N}H_3 + \overset{\ominus}{I}$$

$$\ddot{N}H_3 + R—OTs \xrightarrow{S_N2} R—\overset{\oplus}{N}H_3 + \overset{\ominus}{OTs}$$

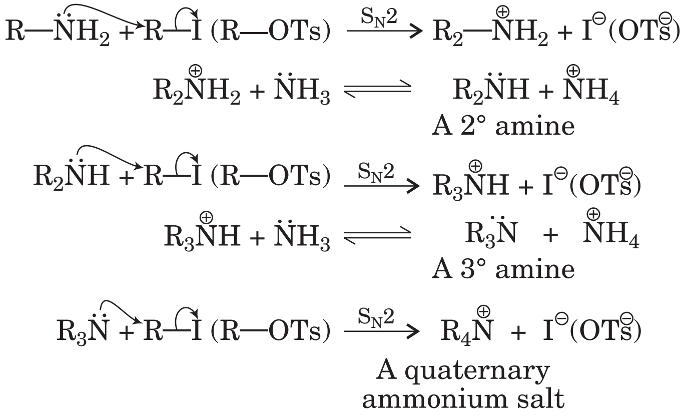
The conjugate acid of the amine then donates an $H^{\oplus}$ to NH_3 liberating the free amine, RNH_2.



$$R{-}\overset{\oplus}{N}H_2{-}H + \ddot{N}H_3 \rightleftharpoons R{-}\ddot{N}H_2 + \overset{\oplus}{N}H_4$$

A 1° amine

The nucleophilic 1° amine can react with more R-I or R-OTs to yield 2° and 3° amines together with same quaternary ammonium salt, resulting in a complex mixture.



$$R{-}\ddot{N}H_2 + R{-}I\ (R{-}OTs) \xrightarrow{S_N2} R_2{-}\overset{\oplus}{N}H_2 + I^{\ominus}(OTs^{\ominus})$$

$$R_2\overset{\oplus}{N}H_2 + \ddot{N}H_3 \rightleftharpoons R_2\ddot{N}H + \overset{\oplus}{N}H_4$$

A 2° amine

$$R_2\ddot{N}H + R{-}I\ (R{-}OTs) \xrightarrow{S_N2} R_3\overset{\oplus}{N}H + I^{\ominus}(OTs^{\ominus})$$

$$R_3\overset{\oplus}{N}H + \ddot{N}H_3 \rightleftharpoons R_3\ddot{N} + \overset{\oplus}{N}H_4$$

A 3° amine

$$R_3\ddot{N} + R{-}I\ (R{-}OTs) \xrightarrow{S_N2} R_4\overset{\oplus}{N} + I^{\ominus}(OTs^{\ominus})$$

A quaternary
ammonium salt

The yield of the 1° amine (RNH_2) can be increased by using a large excess of NH_3 to encourage its collisions with RI or ROTs and to discourage collisions of RI or ROTs with the 1° and 2° amines.

2. Mention the type of halides which cannot be used to alkylate an amine. Give your reasoning.

Solution The following halides cannot be used to alkylate an amine: (i) tertiary halides (due to steric reason they undergo elimination instead of substitution); (ii) vinyl and aryl halides (they do not undergo S_N2 reactions unless activated by *o*- or *p*-substituted election-attracting groups like-NO_2, —NO, etc.) and (iii) neopentyl halides (due to steric hindrance, they do not undergo S_N2 reaction).

3. Give suitable starting compounds from which *n*-butylamine can be prepared by reduction with $LiAlH_4$, H_2/Pt or Na/EtOH.

Solution All the compounds must contain four carbon atoms.

$LiAlH_4$: $CH_3(CH_2)_3NO_2$ (a nitro compound), $CH_3(CH_2)_2CONH_2$ (an amide), $CH_3(CH_2)_2C{\equiv}N$ (a nitrile), $CH_3(CH_2)_2CH{=}NOH$ (an oxime) and $CH_3(CH_2)N_3$ (an azide).

H_2/Pt: $CH_3(CH_2)_3NO_2$, $CH_3(CH_2)_2C{\equiv}N$, $CH_3(CH_2)_2CH{=}NOH$ and $CH_3(CH_2)_3N_3$

Na/EtOH: $CH_3(CH_2)_2C{\equiv}N$ and $CH_3(CH_2)_2CH{=}NOH$

4. **Provide the structures of the products of reductive-amination of (a) $CH_3CH_2CH_2CHO$ and (b) $CH_3CH_2COCH_2CH_3$ with (i) NH_3, (ii) $EtNH_2$ and (iii) Me_2NH.**

Solution

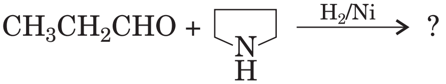
(a) (i) $CH_3(CH_2)_3NH_2$, (ii) $CH_3(CH_2)_3NHEt$, (iii) $CH_3(CH_2)_3NMe_2$

(b) (i) $(CH_3CH_2)CHNH_2$, (ii) $(CH_3CH_2)_2CHNHEt$, (iii) $(CH_3CH_2)_2CHNMe_2$

5. **Mention the advantages of reductive-amination over the reaction of alkyl halides with amines.**

Solution Reductive amination gives the same types of products as does the reaction of amines with alkyl halides. However, successive aminations is more easily controlled in this case. By using a ketone, we get a product containing a *sec*-alkyl group. These amines cannot be easily synthesized by the ammonolysis of the 2° substrate R_2CHX which, because of steric reason, many undergo E2 instead of S_N2.

6. **(a) Provide a reasonable pathway for reductive-amination.**
   (b) Predict the product of the following reaction. What is the intermediate that is reduced?

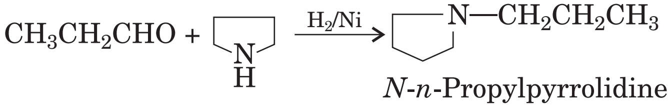


Solution

(a) The reductive-amination takes place in two steps. In the first step, a Schiff base (or enamine) is formed. In the second step, the Schiff base (or enamine) is reduced in situ. Its reduction is relatively by more faster than that of the starting carbonyl compound. For example:

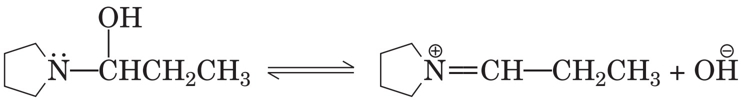
$$Me_2C{=}O + CH_3CH_2NH_2 \xrightleftharpoons{-H_2O} Me_2C{=}N{-}CH_2CH_3 \xrightarrow{\text{Reduction}} Me_2CHNHCH_2CH_3$$

(b)



N-*n*-Propylpyrrolidine

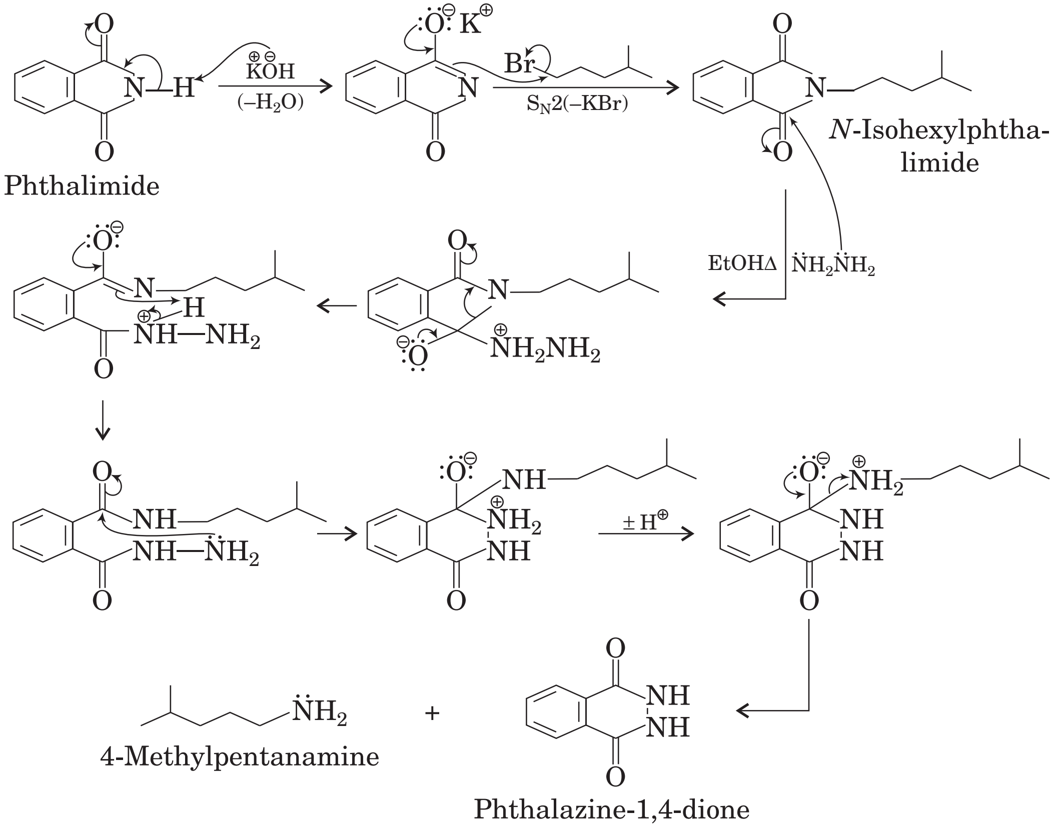
The intermediate is either a carbinolamine or the iminium ion formed from it.



A carbinolamine An iminium ion

7. **Outline a synthesis of 4-methylpentanamine using the Gabriel synthesis. Give mechanisms of the reactions involved.**

Solution



8. **Because of steric reason, *t*-butylamine and neopentylamine cannot be prepared by the action of NH_3 on the corresponding alkyl bromide. Show how can each be prepared from a carboxylic acid.**

Solution A carboxylic acid may be converted into a primary amine by converting it into an amide followed by *Hofmann rearrangement* or *Hofmann degradation*.

Preparation of *t*-butylamine:

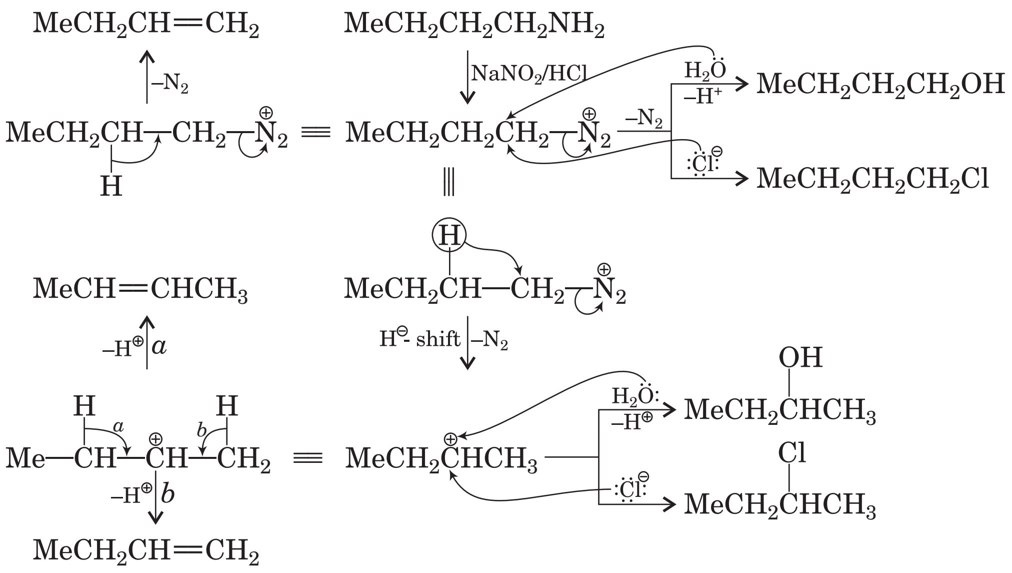
$$\underset{\text{2,2-Dimethylpropanoic acid}}{Me_3CCO_2H} \xrightarrow[\text{2. } NH_3]{\text{1. } SOCl_2} Me_3CCONH_2 \xrightarrow[KOH]{Br_2} \underset{t\text{-Butylamine}}{Me_3CNH_2}$$

Preparation of neopentylamine:

$$\underset{\text{3,3-Dimethylbutanoic acid}}{Me_3CCH_2CO_2H} \xrightarrow[\text{2. } NH_3]{\text{1. } SOCl_2} Me_3CCH_2CONH_2 \xrightarrow[KOH]{Br_2} \underset{\text{Neopentylamine}}{Me_3CCH_2NH_2}$$

9. **When *n*-$BuNH_2$ is subjected to deamination with $NaNO_2$/HCl, two butanols, two butenes and two butyl chlorides are obtained. Give a reasonable mechanism for the formation of these products.**

Solution The following mechanism explains the formation of these products:

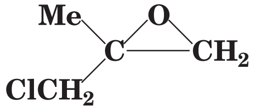


10. Of a group of isomeric amines, the 3° amine has the lowest boiling point. Offer an explanation.

Solution Intermolecular hydrogen bonding rises the boiling point of that compound. Primary (—NH_2) and secondary amines (—NH—) can form hydrogen bonds, but tertiary amines $\left(>N—\right)$ cannot. Therefore, tertiary amines have the lowest b.p. of a group of isomeric amines.

11. Suggest a reasonable mechanism for each of the following reactions:

(a) $MeCOCH_2Cl + CH_2N_2 \longrightarrow ClCH_2COCH_2Me +$

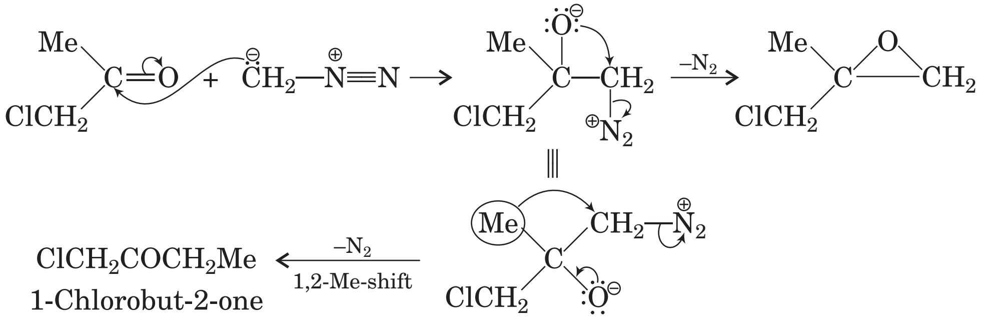


(b) $Me_2C(OH)CH_2CMe_2NH_2 \xrightarrow{HNO_2} Me_2C{=}O + Me_2C{=}CH_2$

(c) $PhCH{=}NHe \xrightarrow[2.\ H_3O^{\oplus}]{1.\ MeI} PhCHO + MCNHMe$

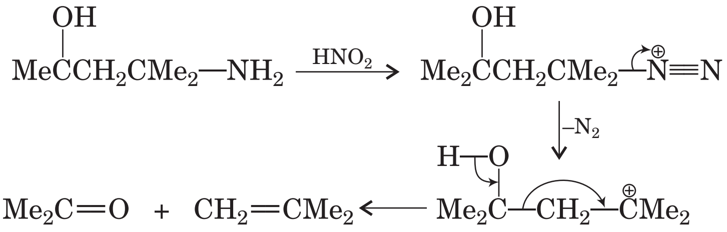
Solution

(a)



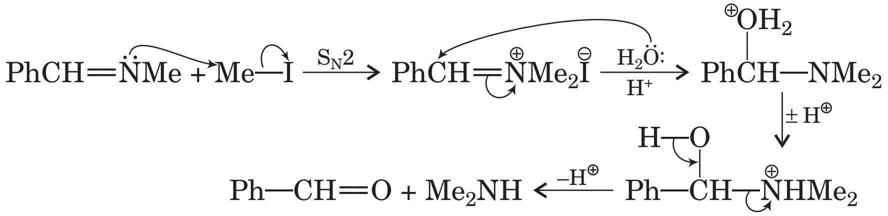
The migratory aptitude increases with increasing the electron-releasing property of that group. Since Me has a +I effect and $ClCH_2$ a –I effect, the former migrates preferentially to give 1-chlorobut-2-one instead of 4-chlorobut-2-one

(b)



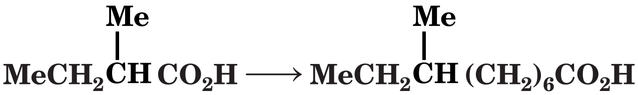
Due to the presence of a β-OH group, the carbocation undergoes fission more easily (than removal of a proton) to give acetone and 2-methylpropene.

(c)



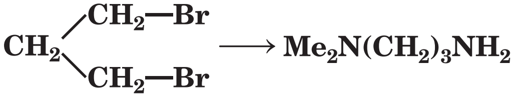
12. How would you carry out the following transformations?

(a)



$$\mathbf{MeCH_2\overset{Me}{\overset{|}{C}H}\,CO_2H \longrightarrow MeCH_2\overset{Me}{\overset{|}{C}H}\,(CH_2)_6CO_2H}$$

(b)

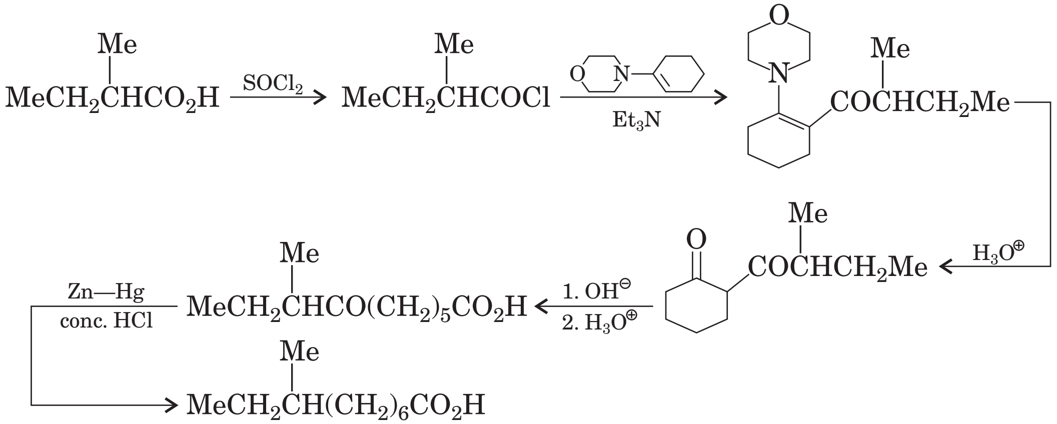


(c) $\mathbf{O_2NCH_2CH_2CH_2CN \longrightarrow (CH_2)_4(NH_2)_2}$

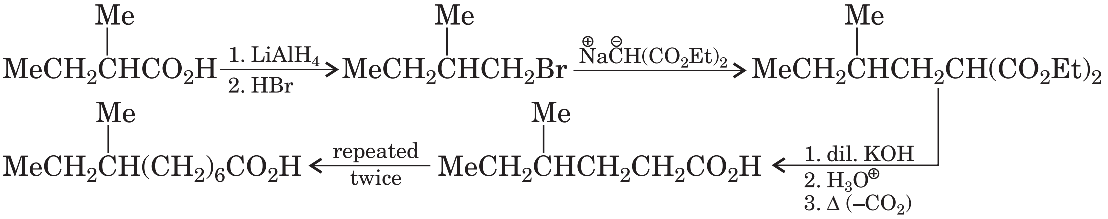
(d) $\mathbf{O_2NCH_2CH_2CH_2CN \longrightarrow O_2N(CH_2)_4NH_2}$

Solution

(a)



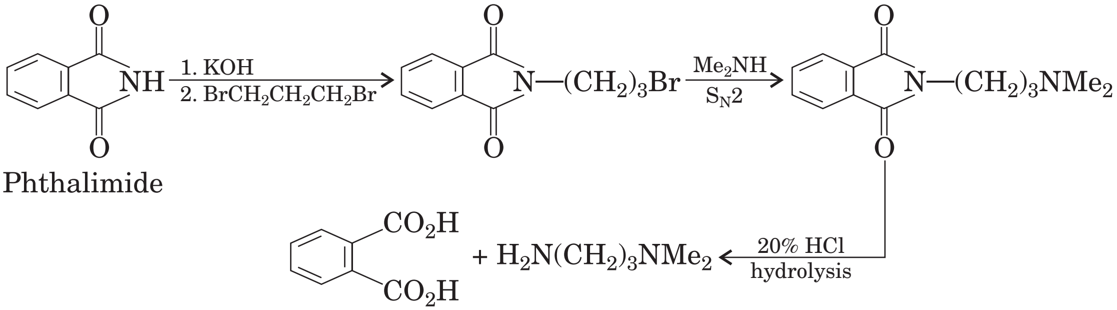
Since the length of the chain has been increased by six carbon atoms, a cyclohexene-enamine is used in the second step of this transformation.
This conversion may be carried out by the standard method of stepping up the acid series by two carbon atoms at a time using diethyl malonate (DEM).



$$\mathrm{MeCH_2\overset{Me}{C}HCO_2H \xrightarrow[2.\ HBr]{1.\ LiAlH_4} MeCH_2\overset{Me}{C}HCH_2Br \xrightarrow{\overset{\oplus}{Na}\overset{\ominus}{C}H(CO_2Et)_2} MeCH_2\overset{Me}{C}HCH_2CH(CO_2Et)_2}$$

$$\mathrm{MeCH_2\overset{Me}{C}H(CH_2)_6CO_2H \xleftarrow[twice]{repeated} MeCH_2\overset{Me}{C}HCH_2CH_2CO_2H \xleftarrow[2.\ H_3O^{\oplus}\ \ 3.\ \Delta\ (-CO_2)]{1.\ dil.\ KOH}}$$

(b) This transformation may be carried out by using Gabriel synthesis.

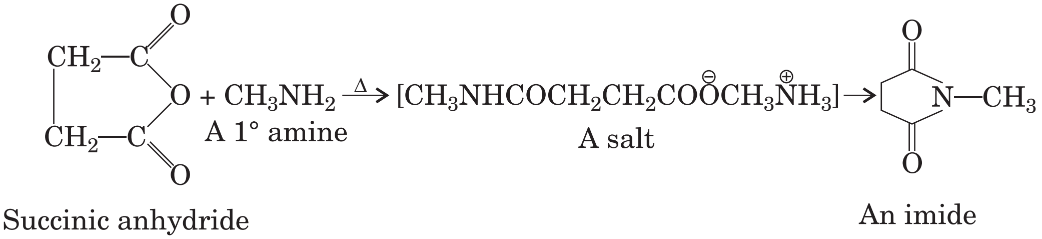


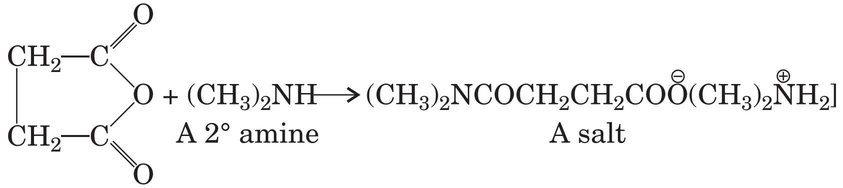
(c) $\mathrm{O_2NCH_2CH_2CH_2CN \xrightarrow{LiAlH_4} H_2NCH_2CH_2CH_2CH_2NH_2}$

(d) $\mathrm{O_2NCH_2CH_2CH_2CN \xrightarrow[AlCl_3]{NaBH_4} O_2NCH_2CH_2CH_2CH_2NH_2}$

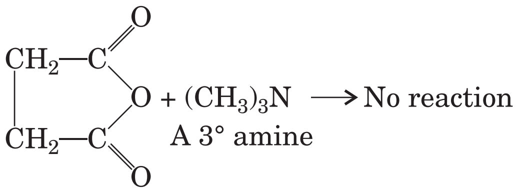
13. How can you distinguish among CH_3NH_2 (a 1° amine), $(CH_3)_2NH$ (a 2° amine) and $(CH_3)_3N$ (a 3° amine) using succinic anhydride?

Solution When CH_3NH_2 is hated with succinic anhydride, an imide is formed which is insoluble in H_2O and $H_3O^{\oplus}$.

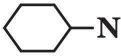




A salt is obtained which does not form an imide when heated, and is soluble in water.



The unreacted amine dissolves in dilute acid.

14. How would you distinguish between (a) *m*-$ClC_6H_4NH_2$ and $Ph\overset{\oplus}{N}H_3Cl^{\ominus}$, (b)  **—NH_2 and $PhNH_2$, (c) $PhNHCOCH_3$ and $PhNH_2$, (d) $Me_4\overset{\oplus}{N}Cl^{\ominus}$ and $Me_3\overset{\oplus}{N}HCl^{\ominus}$, and (e) $Me_4\overset{\oplus}{N}OH^{\ominus}$ and Me_2NCH_2OH?**

Solution

(a) When a solution of $AgNO_3$ is added to the chloride salt $Ph\overset{\oplus}{N}H_3Cl^{\ominus}$, a white precipitate is immediately obtained.

$$Ph\overset{\oplus}{N}H_3Cl^{\ominus} + AgNO_3 \longrightarrow \underset{\text{(white)}}{AgCl\downarrow} + Ph\overset{\oplus}{N}H_3NO_3^{\ominus}$$

The other compound does not react with $AgNO_3$.

(b) Both compounds form a diazonium salt with $NaNO_2$/HCl at 0–5°C. However, the salt $Ph\overset{\oplus}{N}_2Cl^{\ominus}$ is more stable and gives a highly coloured azo compound (the so-called red dye) with alkaline β-naphthol. The salt cyclohexyl $-\overset{\oplus}{N}_2Cl^{\ominus}$, on the other hand, is unstable and liberates N_2 detected by its bubbles.

(c) Unlike acetanilide ($PhNHCOCH_3$), aniline ($PhNH_2$) is basic and readily dissolves in dil. HCl forming a hydrochloride salt.

(d) When $Me_3\overset{\oplus}{N}HCl^{\ominus}$ is heated with conc. NaOH solution, the volatile-free base Me_3N is liberated. It is detected by the typical ammonia-like odour. The other compound does not react with conc. NaOH solution.

(e) Being a strong base aqueous $Me_4\overset{\oplus}{N}OH^{\ominus}$ turns red litmus blue. It also produces a white precipitate of $Ba(OH)_2$ with $BaCl_2$ solution. The other compound is a covalent aminoalcohol, and so, it does not respond to these tests.

Study Problems

1. Which of the following amines can be prepared by the Gabriel synthesis? Which ones cannot? Give your reasoning.

(a) Isobutylamine
(b) *p*-Toluidine
(c) *N*-Ethylbenzylamine
(d) 2-Phenylethylamine
(e) *tert*-Butylamine
(f) *n*-Butylamine

[**Hint:** (a), (d) and (f) can be prepared by this method.]

2. Outline synthesis of each of the following aryl-amines from benzene:
   (a) *m*-Aminoacetophenone (b) *p*-Bromoaniline
   (c) *p*-Isopropylaniline (d) *N*-Ethylaniline
   (e) 4-Isopropyl-1,3-benzenediamine

3. Deamination of 2,2-dimethyl propylamine, $Me_3CCH_2NH_2$, by HNO_2 gives the same products as being formed from 1,1-dimethylpropylamine, $CH_3CH_2C(CH_3)_2NH_2$. Suggest a mechanistic explanation for the formation of common products from these two amines.

4. MeCONHMe does not undergo the Hofmann amine preparation reaction, offer an explanation.

5. Identify A through E in the following sequence of reactions:

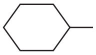
$$PhSO_2Cl + CH_3CH_2CH_2NH_2 \xrightarrow{-HCl} A \xrightarrow{NaOH} B \xrightarrow{EtBr} C \xrightarrow{H_3O^{\oplus}} D + E$$

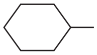
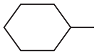
6. When (*R*)-2-methylbutanamide is treated with Br_2/KOH, an optically active amine is obtained. Give the structure of the amine including its stereochemical designation and the mechanism for its formation.

7. Predict the product expected to be formed when phenol is allowed to react with HCHO and Me_2NH.
[**Hint:** This reaction (aminoalkylation) is a special case of the Mannich reaction.]

8. What kind of reagents are to be used to form the conjugate base of an amine?
[**Hint:** Strongly basic compounds such as *n*-BuLi, NaH or RMgX and active metals such as Na or K.]

9. Explain the following observations:
   (a) *N*-Nitrosoamines (RNHN=O) are insoluble in aq. HCl.
   (b) An amine (RNH_2) is more basic than an imine (RCH=NR) which, in turn, is more basic than a nitrile ($RC\equiv N:$).
   (c) Aniline cannot be prepared by Gabriel synthesis.
   (d) Formic acid acts as a reducing agent in the *Esch weiler-Clarke Synthesis*.
   (e) (*S*)-2-Methylbutanamide reacts to Br_2/KOH to form (*S*)-*sec*-butylamine.
   (f) Aryldiazonium ions are more stable than alkyldiazonium ions.
   (g) $Me_3\overset{\oplus}{N}CH_2CH_2NH_2$ is a weaker base than $Me_3CCH_2CH_2NH_2$.

10. Compare the basicities of (a) $HC\equiv CCH_2NH_2$, $CH_2=CHCH_2NH_2$ and $CH_3CH_2CH_2NH_2$ and (b) $PhCH_2NH_2$, p-$NO_2C_6H_4CH_2NH_2$ and $-CH_2NH_2$.

11. How would you carry out each of the following transformations?
   (a) $Me_3CCl \longrightarrow (CH_3)_3CCH_2NH_2$
   (b) $CH_3CH_2CH_2CH_2OH \longrightarrow CH_3CH_2CH_2CH_2CH_2NH_2$
   (c) $-OH \longrightarrow$ $-NHCH_3$
   (d) $CH_3CHOHCH_3 \longrightarrow CH_3CHOHCH_2NH_2$
   (e) $CH_3CHOHCH_3 \longrightarrow CH_3CHOHCH_2NMe_2$

12. Write down the three isomeric amines represented by the molecular formula, C_3H_9N. How can these amines be distinguished by a chemical method?

1.4 NITRO COMPOUNDS (ALIPHATIC AND AROMATIC)

1.4.1 Preparations

1.4.1.1 Preparations of Aliphatic Nitro Compounds or Nitro-alkanes

1. From alkyl halide When a primary or secondary alkyl halide (mainly RBr or RI) dissolved in dimethyl formamide (DMF) is allowed to react with sodium nitrite, a nitroalkane is obtained. To increase the solubility of $NaNO_2$, some urea is added to the reaction medium. If dimethyl sulphoxide (DMSO) is used as a solvent, the addition of urea is unnecessary. A small amount of alkyl nitrite is also obtained.

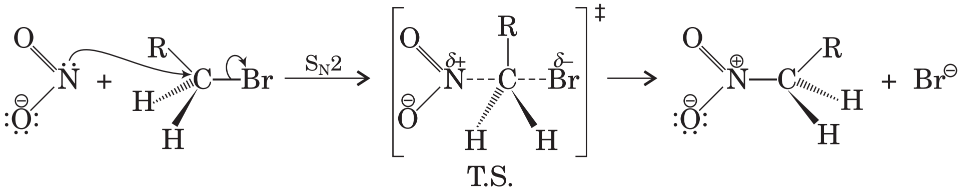
$$\underset{1^\circ \text{ or } 2^\circ}{R{-}Br} + NaNO_2 \xrightarrow[\text{or DMSO}]{\text{DMF + Urea}} \underset{\substack{\text{Nitroalkane}\\ \text{(major)}}}{R{-}NO_2} + \underset{\substack{\text{Alkyl nitrite}\\ \text{(minor)}}}{R{-}ONO} + NaBr$$

Primary nitroalkanes can also be prepared by heating on alkyl halide with silver nitrate in aqueous ethanolic solution:

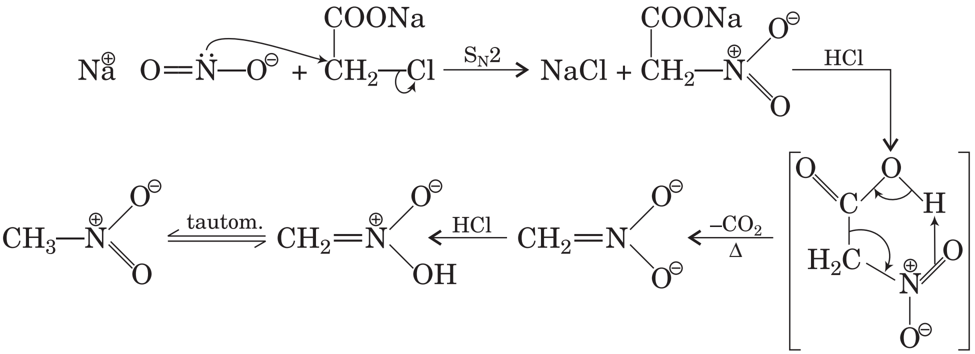
$$\underset{1^\circ}{RX} + AgNO_2 \xrightarrow[\text{ethanol}]{\text{aqueous}} \underset{\text{(major)}}{RNO_2} + \underset{\text{(minor)}}{RONO} + AgX$$

Mechanism:

When the reaction is carried out with $NaNO_2$ in DMF or DMSO, the reaction takes place by an S_N2 mechanism. $NO_2^{\ominus}$ is an ambident nucleophile which can attack a substrate through nitrogen or oxygen atom. Since the N-atom is relatively larger and less electronegative, i.e., more polarisable than the O-atom, attack by $NO_2^{\ominus}$ on carbon occurs through nitrogen to yield nitroalkane as the major product.



2. From α-halogeno acids When the sodium salt of an α-halogeno acid is heated with an aqueous solution of sodium nitrite and the resulting mixture is acidified, an α-nitro acid is obtained. The nitro acid, when heated, eliminates CO_2 to produce a nitroalkane. For example:



3. By vapour phase nitration of alkanes When a mixture of gaseous alkane and HNO_3 vapour is heated to 400–475°C, nitroalkanes are obtained. For example:

$$CH_4 + HNO_3 \xrightarrow{400°C} CH_3NO_2\ \text{(Nitromethane)} + H_2O$$

Alkanes containing two or more carbon atoms undergo C—C bond cleavage to produce a mixture of nitroalkanes. For example:

$$\underset{\text{Ethane}}{CH_3—CH_3} + HNO_3 \xrightarrow{400°C} \underset{\text{Nitroethane}}{CH_3CH_2NO_2} + \underset{\text{Nitromethane}}{CH_3NO_2}$$

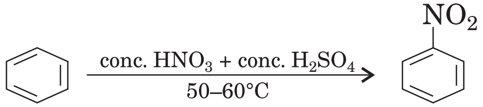
1.4.1.2 Preparations of Aromatic Nitro Compounds

1. By nitration of aromatic compounds Aromatic nitro compounds are prepared by nitrating a suitable aromatic compound with any one of the following nitrating agents.

(a) mixed acid (conc. HNO_3 + conc. H_2SO_4 or fuming HNO_3 + conc. H_2SO_4 or fuming HNO_3 + fuming H_2SO_4), (b) conc. HNO_3 dissolved in glacial acetic acid or nitromethane, (c) acetyl nitrate (conc. HNO_3 dissolved in acetic anhydride) and (d) nitronium salt dissolved in organic solvents (e.g., nitronium perchlorate, $NO_2^{\oplus}ClO_4^{\ominus}$; nitronium tetrafluroborate, $\overset{\oplus}{N}O_2BF_4^{\ominus}$, etc.).

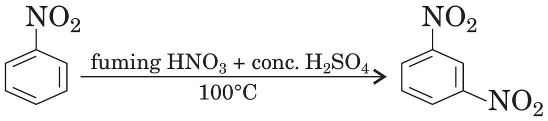
Examples:

(i)



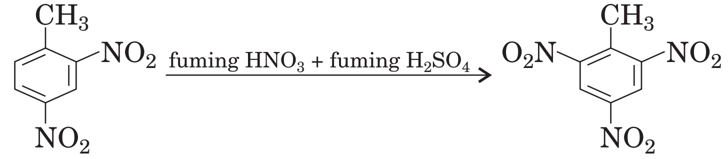
Benzene Nitrobenzene

(ii)



Nitrobenzene *m*-Dinitrobenzene

(iii)



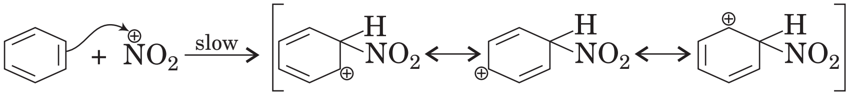
2,4-Dinitrotoluene 2,4,6-Trinitrotoluene

Mechanism of the reaction: In this electrophilic aromatic substitution, the nitronium ion ($\overset{\oplus}{N}O_2$) acts as an electrophile.

$$HO{-}NO_2 + 2H_2SO_4 \rightleftharpoons \overset{\oplus}{N}O_2 + H_3O^{\oplus} + 2HSO_4^{\ominus}$$

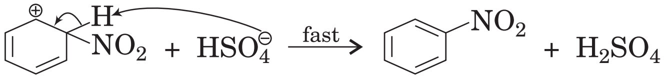
The reaction proceeds through the steps as follows:

Step 1:



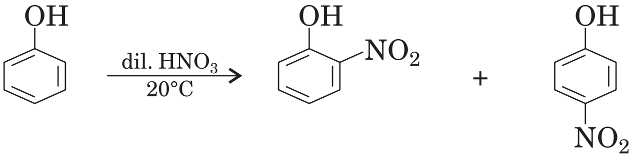
σ-complex

Step 2:



Nitrobenzene

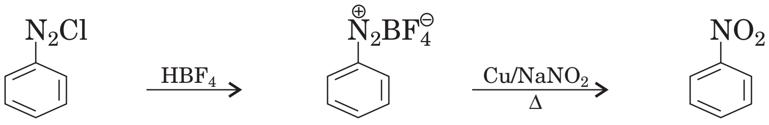
It is to be noted that the presence of hydroxyl group (–OH) in the benzene ring activates the ring to such an extent that treatment of phenol even with dilute HNO_3 at ordinary temperature gives a mixture of *o*- and *p*-nitrophenol.



Phenol *o*-Nitrophenol *p*-Nitrophenol

2. From diazonium salts Fluoroboric acid reacts with arenediazonium chloride to form arenediazonium fluoroborate. The resulting salt is then decomposed in the presence of aqueous solution of $NaNO_2$ and Cu powder to yield the corresponding nitro compound.

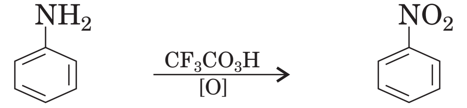
Example:



Benzenediazonium chloride Benzenediazonium fluoroborate Nitrobenzene

3. From aromatic amines Aromatic amines can be oxidized by trifluoroperacetic acid to the corresponding nitro compounds.

Example:



1.4.2 Reactions

1.4.2.1 Reactions of Aliphatic Nitro Compounds

1. Reduction Nitroalkanes undergo reduction through the following steps:

$$\underset{\text{Nitro compound}}{R—NO_2} \longrightarrow \underset{\text{Nitroso compound}}{R—N{=}O} \longrightarrow \underset{\text{Substituted hydroxylamine}}{R—NHOH} \longrightarrow \underset{1^\circ\ \text{Amine}}{RNH_2}$$

The nature of the product depends on the reducing agent used and the pH of the reaction medium.

- **Reduction in acid medium:** Reduction of nitroalkanes with Sn, Fe or Zn and concentrated HCl gives primary amines.

  Example:

  $$\underset{\text{Nitromethane}}{CH_3NO_2} \xrightarrow[\text{or Zn/HCl}]{\text{Sn/HCl or Fe/HCl}} \underset{\text{Methylamine}}{CH_3NH_2}$$

- **Reduction in neutral medium:** Nitroalkanes, when reduced by heating with zinc dust, NH_4Cl and 50% EtOH, yield *N*-alkylhydroxylamine.

  Example:

  $$\underset{\text{Nitroethane}}{C_2H_5NO_2} \xrightarrow[\text{50\% EtOH}/\Delta]{\text{Zn dust}/NH_4Cl} \underset{N\text{-Ethylhydroxylamine}}{C_2H_5NHOH}$$

- **Identification of nitroalkanes by Mulliken–Barker test:** The nitro compound is boiled with zinc dust and NH_4Cl in 50% ethanol. The resulting solution is filtered into a freshly prepared Tollens' reagent. Appearance of a black or grey precipitate or a silver mirror indicates the presence of a $–NO_2$ group.

$$RNO_2 + 4H \longrightarrow RNHOH + H_2O$$

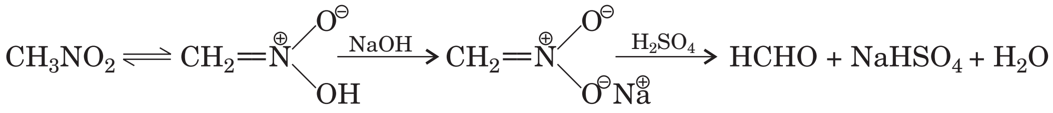
$$RNHOH + 2[Ag(NH_3)_2]OH \longrightarrow RNO + 2Ag\downarrow + 4NH_3 + 2H_2O$$

This test is applicable also to the aromatic nitro compounds.

2. Nef carbonyl synthesis When the sodium salt of the acinitro form of 1° and 2° nitroalkanes are treated with 50% H_2SO_4 at room temperature, aldehydes and ketones are obtained respectively. Tertiary nitro-alkanes do not undergo this reaction due to lack of α–H atom.

Examples:

(i)



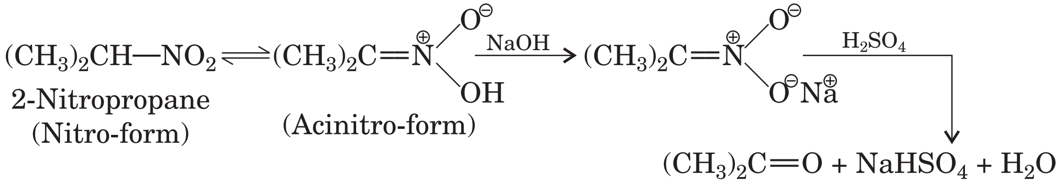
$$CH_3NO_2 \rightleftharpoons CH_2{=}\overset{\oplus}{N}(O^{\ominus})(OH) \xrightarrow{NaOH} CH_2{=}\overset{\oplus}{N}(O^{\ominus})(O^{\ominus}Na^{\oplus}) \xrightarrow{H_2SO_4} HCHO + NaHSO_4 + H_2O$$

Nitromethane (Nitro-form)

(Acinitro-form)

Formaldehyde

(ii)



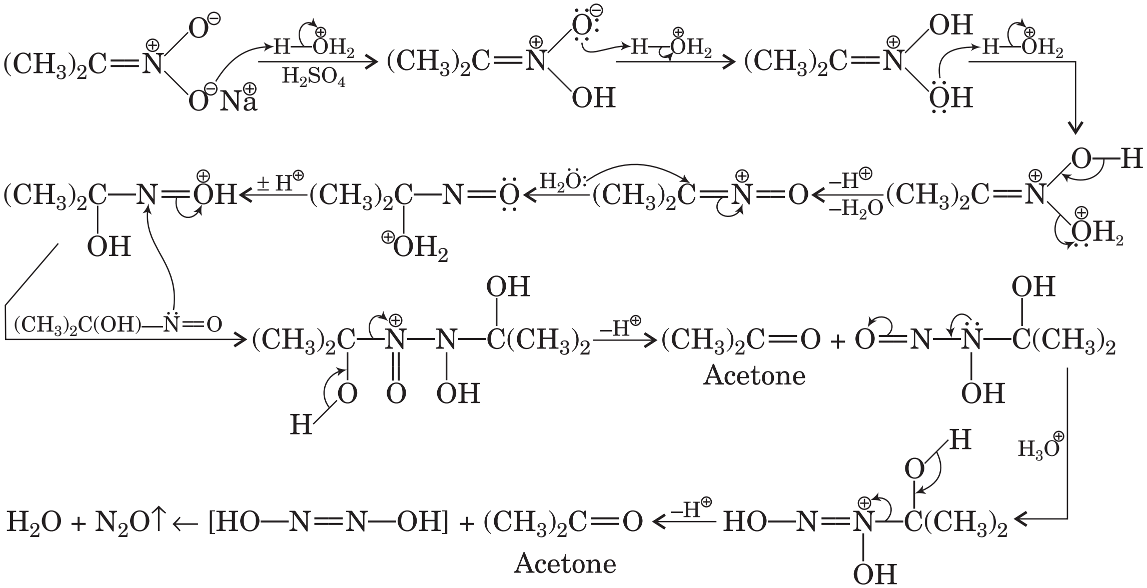
$$(CH_3)_2CH{-}NO_2 \rightleftharpoons (CH_3)_2C{=}\overset{\oplus}{N}(O^{\ominus})(OH) \xrightarrow{NaOH} (CH_3)_2C{=}\overset{\oplus}{N}(O^{\ominus})(O^{\ominus}Na^{\oplus}) \xrightarrow{H_2SO_4} (CH_3)_2C{=}O + NaHSO_4 + H_2O$$

2-Nitropropane (Nitro-form)

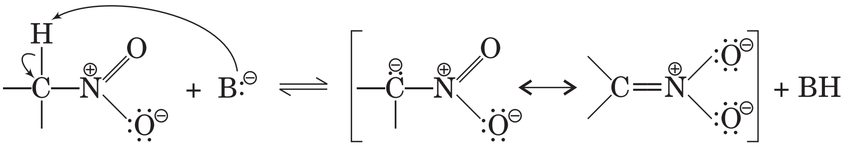
(Acinitro-form)

Acetone

Mechanism of the reaction:



3. Henry reaction Anions adjacent to a nitro group have many similarities to enolate anions. They are formed using similar bases and are stabilized by delocalization of charge onto an electronegative atom.

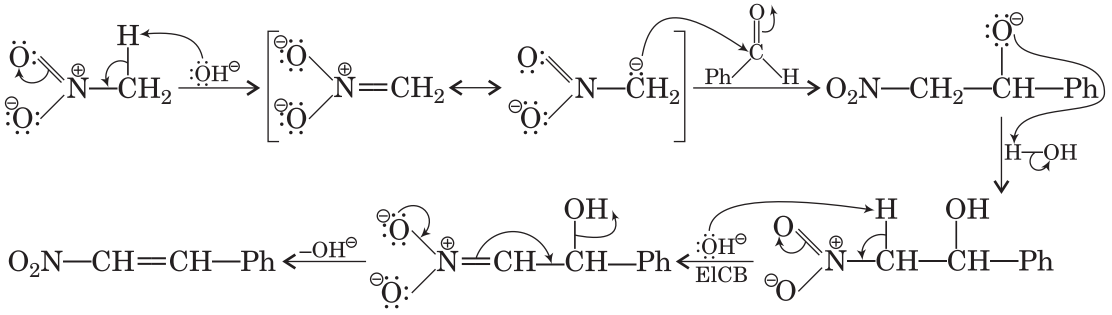


These anions can add to a carbonyl group in a process similar to mixed aldol reaction. Addition produces a hydroxy compound usually dehydrates to give an α,β-unsaturated nitro compound. This nitroaldol reaction is known as *Henry reaction*.

Example:

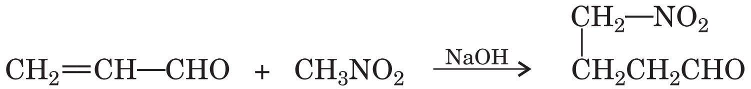
$$CH_3NO_2 + PhCHO \xrightarrow{NaOH/H_2O} PhCH{=}CHNO_2$$

Mechanism of the reaction:



4. Michael addition The conjugate base of a nitroalkane reacts with an α,β-unsaturated carbonyl compound to produce a Michael addition product.

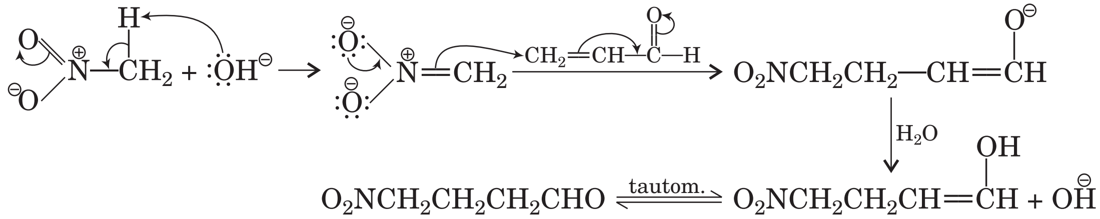
Example:



$$\underset{\text{Aeraldehyde}}{CH_2{=}CH—CHO} + \underset{\text{Nitromethane}}{CH_3NO_2} \xrightarrow{NaOH} \underset{\text{Michael addition product}}{\overset{CH_2—NO_2}{\overset{|}{CH_2CH_2CHO}}}$$

Aeraldehyde Nitromethane Michael addition product

Mechanism of the reaction:

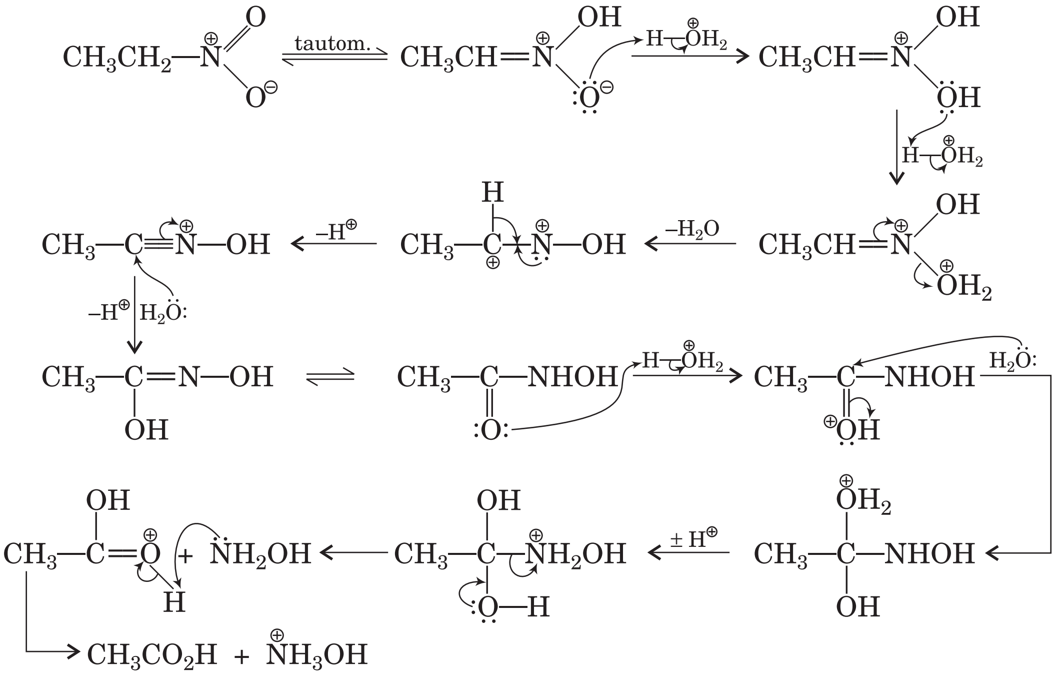


5. Hydrolysis (i) When a primary nitroalkane is boiled with concentrated HCl or 85% H_2SO_4, it undergoes hydrolysis to yield a carboxylic acid and hydroxylamine. This is the most simple and cheapest process for the manufacture of hydroxylamine (NH_2OH).

Example:

$$CH_3CH_2NO_2 \xrightarrow[\text{or 85\% } H_2SO_4 \text{ heat}]{\text{conc. HCl}} CH_3CO_2H + NH_2OH \text{ (salt)}$$

Mechanism of the reaction:



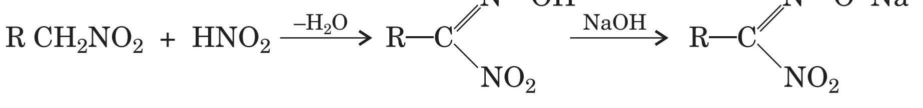
(i) Secondary nitroalkanes are reduced by boiling with conc. HCl to produce ketones and nitrous acid.

$$2Me_2CHNO_2 \xrightarrow[\Delta]{\text{conc. HCl}} 2Me_2C{=}O + N_2O + H_2O$$

(ii) Tertiary nitroalkanes do not undergo hydrolysis by conc. HCl or conc. H_2SO_4.

6. Reaction with nitrous acid Primary, secondary and tertiary nitroalkanes can be differentiated by their reactions with nitrous acid as follows:

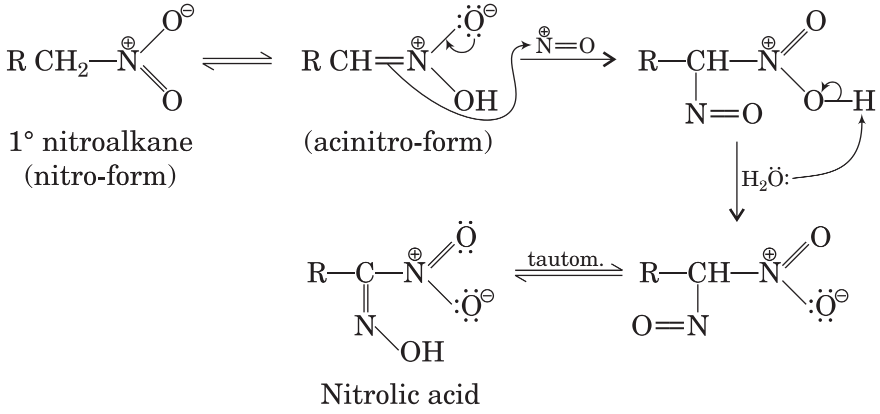
(i) Primary nitroalkanes react with HNO_2 to form nitrolic acid (a crystalline compound) which dissolves in NaOH to give a red solution.



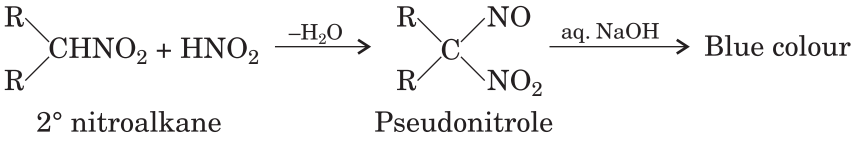
1° nitroalkane Nitrolic acid (a red-coloured salt)

Mechanism of the reaction:

$$HO{-}N{=}O \xrightleftharpoons{H^{\oplus}} H_2\overset{\oplus}{O}{-}N{=}O \xrightleftharpoons{-H_2O} \overset{\oplus}{N}O$$



(ii) A secondary nitroalkane reacts with nitrous acid to form pseudonitrole. It is a colourless crystalline compound which dissolves in sodium hyroxide to give a blue solution. The nitroso group (–NO) present in pseudonitrole may be responsible for the blue colour.



(iii) A tertiary nitroalkane does not reacts with nitrous acid due to lack of α-H atom.

1.4.2.2 Reactions of Aromatic Nitro Compounds

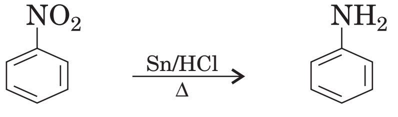
1. Reactions of nitro group The most important reaction of the nitro group in nitrobenzene is its reduction. This takes place through the following steps:

$$Ph\text{-}NO_2 \longrightarrow Ph\text{-}N{=}O \longrightarrow PhNHOH \longrightarrow PhNH_2$$

Nitrobenzene Nitrosobenzene Phenyl hydroxyl-amine Aniline

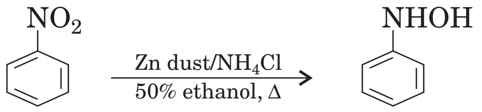
The nature of the product depends on the reducing agent and the concentration of hydrogen ions in the reaction medium.

- **Reduction in acidic medium:** Sn/HCl, Fe/HCl or Zn/HCl or ACOH reduces nitrobenzene to aniline.



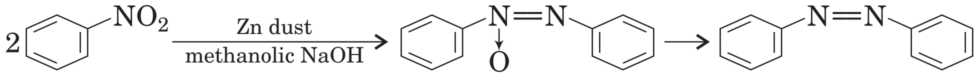
Nitrobenzene Aniline

- **Reduction in neutral medium:** When nitrobenzene dissolved in 50% ethanol is warmed with Zn dust and NH_4Cl, it is reduced to phenylhydroxylamine.



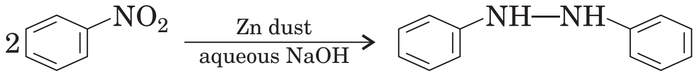
Nitrobenzene Phenylhydroxylamine

- **Reduction in alkaline medium:** Depending on the nature of reducing agents, nitrobenzene gives different reduction products such as azoxybenzene, azobenzene and hydrazobenzene.
  - (i) When nitrobenzene is reduced by zinc dust and methanolic solution of NaOH, initially azoxybenzene and finally azobenzene are obtained.



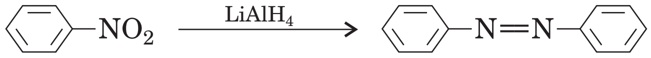
Nitrobenzene Azoxybenzene Azobenzene

  - (ii) When nitrobenzene is reduced by Zn dust and aqueous solution of NaOH, hydrazobenzene is obtained.



Nitrobenzene Hydrazobenzene

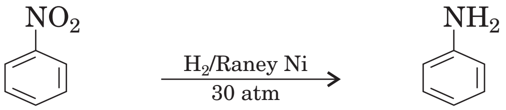
- **Reduction by LiAlH$_4$:** Lithium aluminium hydride reduces nitrobenzene to yield azobenzene.



Nitrobenzene Azobenzene

It is to be noted that the reduction of aliphatic nitro compounds with LiAlH$_4$ gives the corresponding amines.

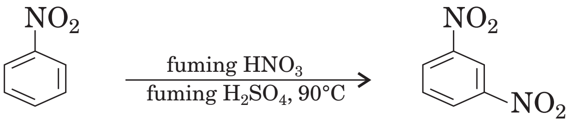
- **Hydrogenation:** Catalytic hydrogenation of nitrobenzene under pressure gives aniline.



Nitrobenzene Aniline

2. Substitution reaction in benzene ring Since the nitro group (–NO$_2$) is *meta*-directing, in electrophilic substitution, the incoming substituent enters mainly at the *meta*-position. The rate of electrophilic substitution in nitrobenzene is much slower than that in benzene because the electron-attracting –NO$_2$ group reduces the electron density of the ring.

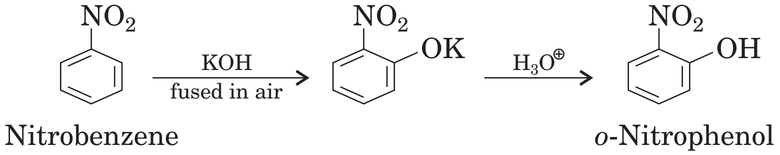
Example:



Nitrobenzene *m*-Dinitrobenzene

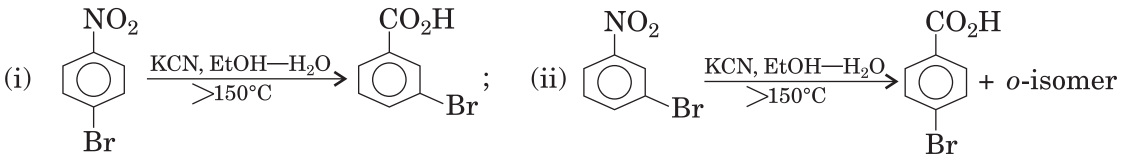
Because of decreased electron density of the ring, nitrobenzene undergoes nucleophilic substitution reaction. Attack by the nucleophile occurs easily at the relatively electron-deficient *ortho*- and *para*-positions.

Example:

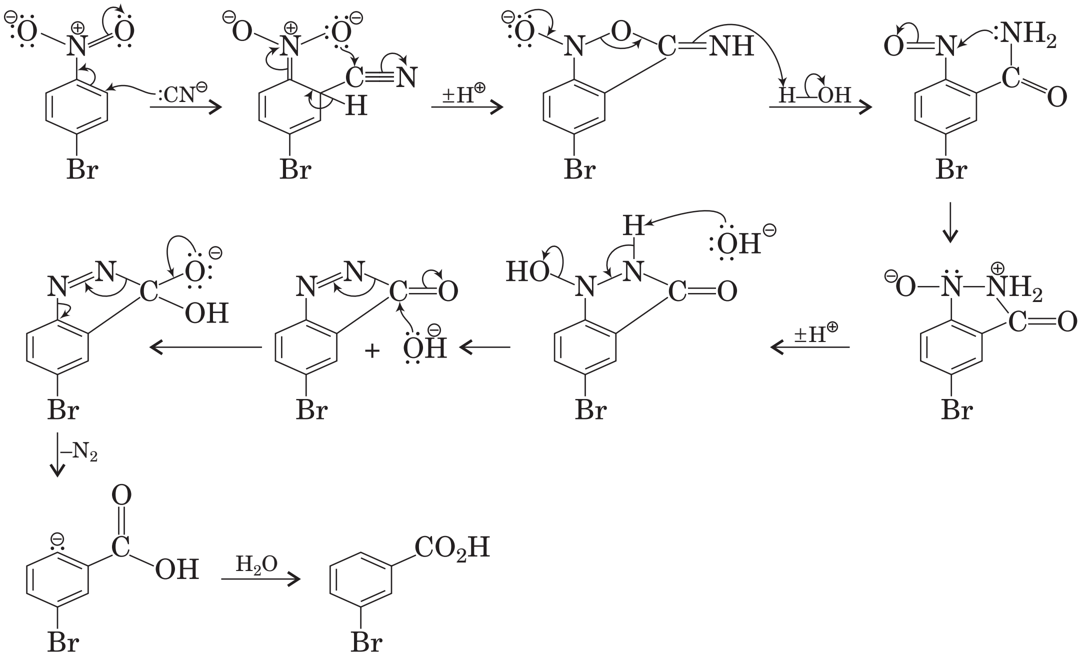


von Richter reaction (*a nucleophilic substitution with rearrangement*) When a *meta*- or *para*-nitrohalobenzene is heated with aqueous-alcoholic potassium cyanide above 150°C, the –NO_2 group is lost and a –COOH group is introduced at the position *ortho* to the –NO_2 group (a *cine* substitution). This nucleophilic substitution with rearrangement is called *von Richter reaction*.

Examples:



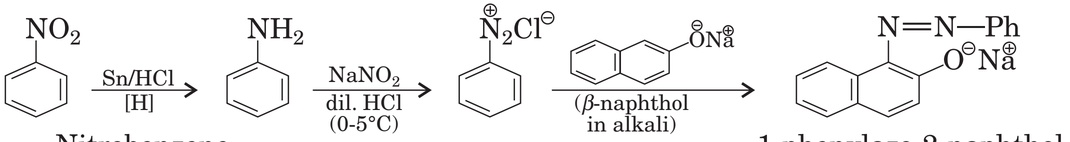
Mechanism of the reaction: The mechanism of the reaction involves the steps as follows:



m-Bromobenzoic acid

Detection of aromatic –NO_2 group using nitrobenzene

1. Reduction test When nitrobenzene is reduced by heating with Sn and conc. HCl, aniline is obtained. The resulting solution is diazotized. A few drops of this solution is added to cold alkaline solution of *β*-naphthol when a bright, scarlet red-azo dye is obtained.



Nitrobenzene

1-phenylazo-2-naphthol
(salt)
[red azo-dye]

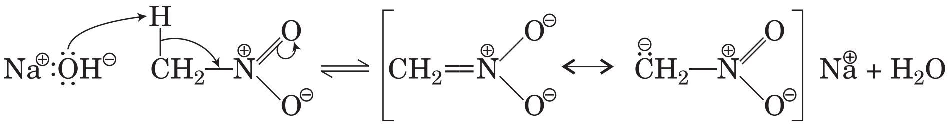
It is a test for the identification of aromatic primary amino (–NH_2) group. As the –NO_2 group is reduced to –NH_2 group, it may be regarded as an indirect test for the detection of –NO_2 group in the benzene ring. *This test cannot be used for the detection of –NO_2 group in the presence of –NH_2 group.*

2. Mulliken-Barker test This test (already discussed) can be used for the detection of –NO_2 group, when –NH_2 group is also present in the benzene ring.

SOLVED PROBLEMS

1. Explain why nitromethane is soluble in NaOH solution.

Solution Due to presence of acidic *α*–H (the conjugate base is resonance-stabilized), nitromethane reacts with NaOH to form the corresponding sodio-salt. Because of this, it is soluble in NaOH solution.

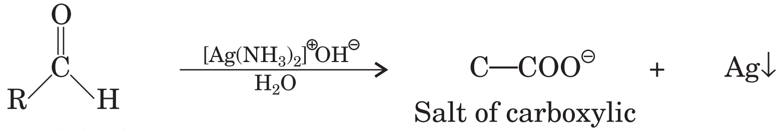


Nitromethane

Conjugate base
(stabilized by resonance)

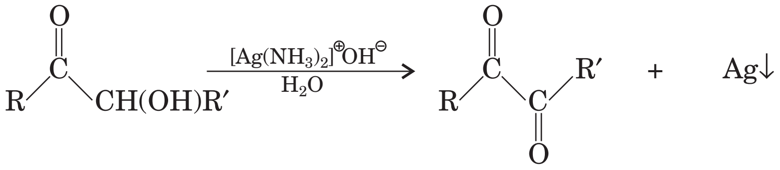
2. Mention an important limitation of the Mulliken–Barker test.

Solution This test for the detection of –NO_2 group is not applicable to an organic compound which already contains any other reducible functional group. For example, if an aldehyde (–CHO) group or an *α*-hydroxyketo [–CH(OH)CO–] group is present in any organic compound, then the Mulliken–Barker test for the identification of –NO_2 group cannot be used and this is because an aldehyde or an *α*-hydroxyketone reduces Tollens' reagent to give a precipitate of silver.



An aldehyde

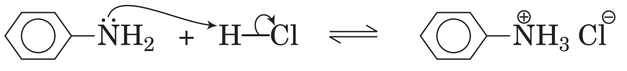
Salt of carboxylic
acid



An α-hydroxyketone A 1,2-diketone

3. **Which out of nitrobenzene and aniline is soluble in dilute HCl and why?**

Solution Unlike nitrobenzene aniline form hydrochloride salt with dil. HCl and because of this it is soluble in dil. HCl.



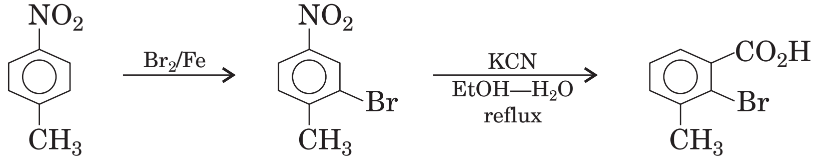
Aniline Aniline hydrochloride (soluble in water)

4. **Why is nitrobenzene not easily oxidized? Mention an important application of nitrobenzene based on this property.**

Solution Due to electron deficiency of the benzene nucleus, nitrobenzene is not oxidized even by strong oxidising agents. Also, due to dipolar nature, its boiling point is much higher. Hence, ritrobenzene can be used as a solvent in oxidation reactions carried out at higher temperature.

5. **How would you prepare 2-bromo-3-methylbenzoic acid which is otherwise very difficult to prepare by usual substitution reaction?**

Solution This can be easily prepared by bromination of *p*-nitrotolune followed by the von Richter reaction of the resulting 2-bromo-4-nitrotoluene.



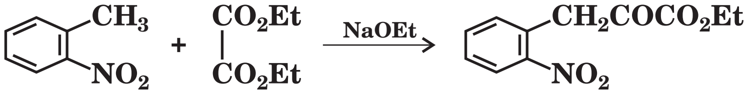
p-Nitroaniline 2-Bromo-4-nitrotoluene 2-Bromo-3-methylbenzoic acid

6. **Suggest a mechanism for each of the following reactions:**

(a) $\mathrm{Me_2CHNO_2 + HCHO + EtNH_2 \xrightarrow{HCl} O_2NCMe_2CH_2\overset{\oplus}{N}H_2EtCl^{\ominus}}$

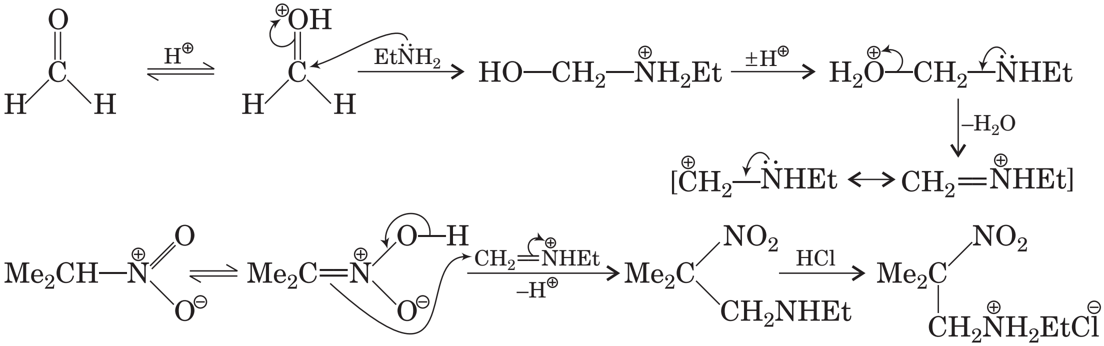
(b) $\mathrm{CH_3NO_2 + HCHO \xrightarrow{OH^{\ominus}/H_2O} HOCH_2CH_2NO_2}$

(c)

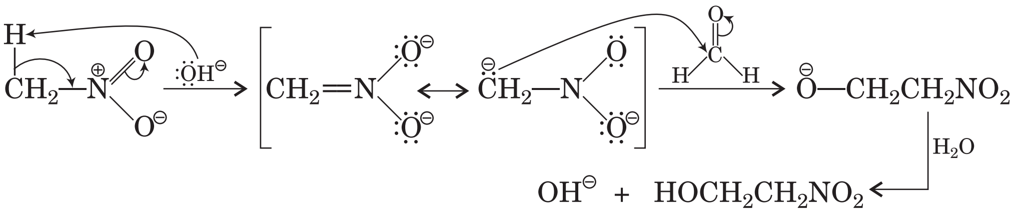


Solution

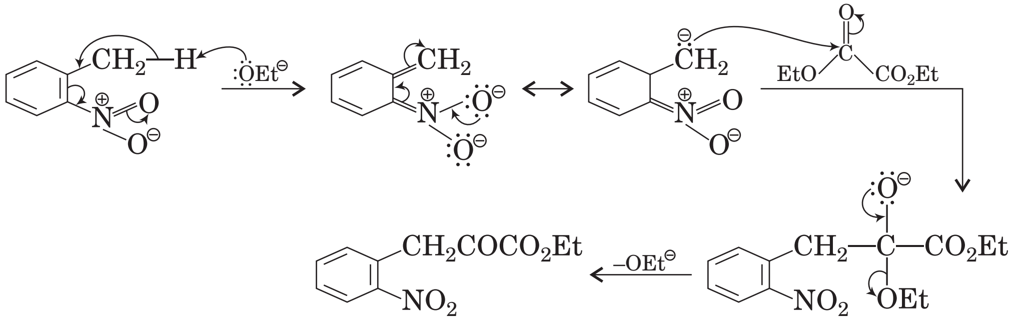
(a)



(b)



(c)



Study Problems

1. Nibrobenzene is a high-boiling liquid—why?
2. 2, 4, 6-Trinitrotoluene can be easily prepared by nitrating tolune. However, it is very difficult to obtain 2, 4, 6-trinitrobenzene by direct nitration of benzene. Explain.
3. How can you detect the $-NO_2$ group is *p*-nitroaniline?
4. When RCl is separately treated with KNO_2 and $AgNO_2$, product compositions differ in major products. Give an explanation.
5. A nitroalkane ($C_3H_7NO_2$) reacts with HNO_2 to form a colourless compound which turns red when NaOH solution is added. Predict the structure of the nitroalkane.
6. How can you demonstrate that nitromethane (CH_3NO_2) the carbon atom is directly linked to the nitrogen atom?

7. Nitromethane is acidic in nature, but trimethylnitro-methane is not. Explain.
8. The $-NO_2$ group in nitrobenzene is *meta*-orienting in electrophilic substitution reaction while it is *ortho*-, *para*-orienting in nucleophilic substitution reaction. Explain.
9. Why does preparation of nitrobenzene necessitate strict control of temperature?

1.5 ALKYL NITRILES AND ISONITRILES

1.5.1 Preparations

Alkyl nitriles or cyanides

1. From alkyl halides Alkyl halides (particularly RI), when heated with ethanolic aqueous solution of KCN or NaCN, yield alkyl cyanides predominantly. A small amount of alkyl isocyanide is also obtained.

Example:

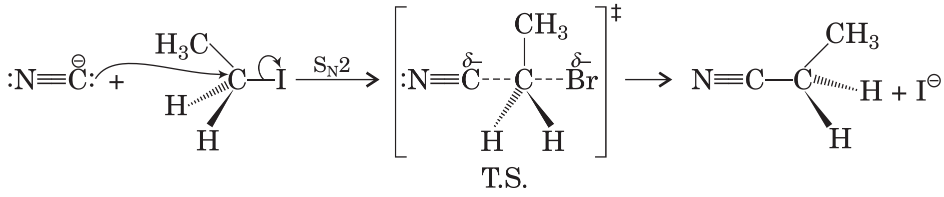
$$C_2H_5I + KCN \xrightarrow[\text{ethanol}]{\text{aqueous}} C_2H_5CN + KI$$

Ethyl iodide Ethyl cyanide

The yield of alkyl nitrile from 1° or 2° alkyl halide is found to be quite satisfactory. However, when 3° alkyl halide is used, mainly alkene is obtained through elimination reaction.

Mechanism of the reaction:

The ambient nucleophile $CN^{\ominus}$ $(:\overset{\ominus}{C}\equiv N:\leftrightarrow :C=\overset{\ominus}{\underset{..}{N}}:)$ attacks the substrate through the more polarisable (less electro-negative and larger in size) carbon atom giving alkyl cyanide or nitrile.



2. From acid amides When acid amides are heated in the presence of phosphorus pentoxide (P_2O_5) or thionyl chloride ($SOCl_2$), alkyl cyanides are obtained.

Example:

$$CH_3CONH_2 \xrightarrow[(-H_2O)]{SOCl_2 \text{ or } P_2O_5/\Delta} CH_3-C\equiv N + H_2O$$

Methyl cyanide

3. From aldoximes When aldoximes are heated with P_2O_5 or acetic anhydride, alkyl cyanides are obtained.

Example:

$$CH_3CH\equiv NOH \xrightarrow[\Delta\ (-H_2O)]{P_2O_5 \text{ or } Ac_2O} CH_3-C\equiv N + H_2O$$

Acetaldoxime Methyl cyanide

4. From carboxylic acids Alkyl cyanides can be prepared on a large scale by passing a mixture of carboxylic acid vapours and NH_3 over alumina heated to 500°C.

Example:

$$\underset{\text{Acetic acid}}{CH_3COOH} + NH_3 \longrightarrow CH_3COONH_4 \xrightarrow[500°C]{Al_2O_3} \underset{\text{Methyl cyanide}}{CH_3CN + 2H_2O}$$

5. From Grignard reagent Cyanogen chloride (ClCN) reacts with Grignard reagents to yield alkyl cyanides. This method is very much suitable for the preparation of tertiary alkyl cyanide because these cannot be prepared from 3° alkylhalide by the action of $CN^{\ominus}$ (S_N2).

Example:

$$\underset{\textit{tert}\text{-Butylmagnesium chloride}}{(CH_3)_3CMgCl} + ClCN \xrightarrow{\text{dry ether}} \underset{\textit{tert}\text{-Butyl cyanide}}{(CH_3)_3CCN} + MgCl_2$$

Alkyl isonitriles or isocyanides

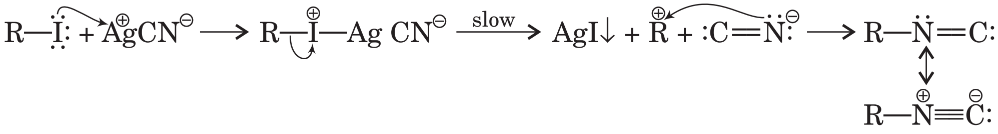
1. From alkyl halides Alkyl isocyanides can be prepared by heating alkyl halides (particularly alkyl bromide or iodide) with aqueous ethanolic silver cyanide solution.

Example:

$$\underset{\text{Isopropyl iodide}}{(CH_3)_2CH{-}I} + AgCN \xrightarrow[\Delta]{H_2O{-}EtOH} \underset{\text{Isopropyl isocyanide}}{(CH_3)_2CH{-}NC} + AgI$$

Mechanism of the reaction:

In the presence of AgCN, silver halide is precipitated, and as a result, a carbocation is formed from RI. The reaction, thus, follows an S_N1 pathway. In the ambient nucleophile $CN^{\ominus}(:\overset{\ominus}{C}\equiv N: \leftrightarrow :C=\overset{\ominus}{\underset{..}{N}}:)$, the smaller and more electronegative N-atom is less polarizable, and therefore, it attacks the carbocation forming an alkyl isocyanide as the major product.

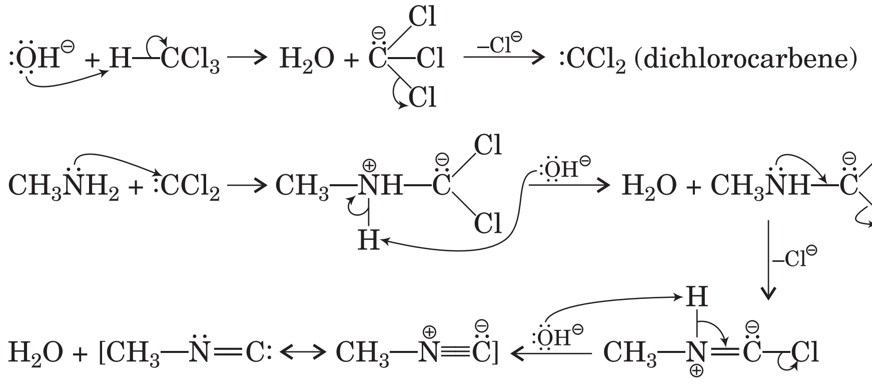


2. From primary amines When primary amines are heated in the presence of chloroform and alcoholic potassium hydroxide solution, alkyl isocyanides are obtained. This reaction is called *carbylamine reaction*.

Example:

$$\underset{\text{Methylamine}}{CH_3NH_2} + CHCl_3 + 3KOH \xrightarrow[EtOH]{\Delta} \underset{\text{Methyl isocyanide}}{CH_3{-}\overset{\oplus}{N}\equiv\overset{\ominus}{C}:} + 3KCl + 3H_2O$$

Mechanism of the reaction:

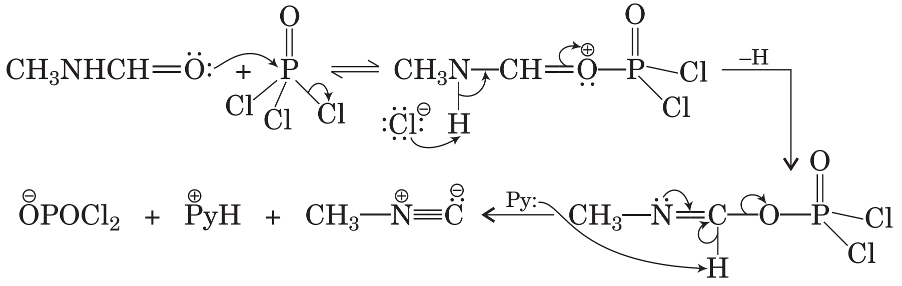


3. From *N*-alkyl formamide When *N*-alkylformanides are dehydrated by phosphorus oxychloride in the presence of pyridine, alkyl isocyanides are obtained.

Example:

$$\underset{N\text{-methyl formamide}}{CH_3NHCHO} \xrightarrow[(-H_2O)]{POCl_3/Pyridine} \underset{\text{Methyl isocyanide}}{CH_3NC}$$

Mechanism of the reaction:



1.5.2 Reactions

Alkyl nitriles or cyanides

1. Hydrolysis Alkyl cyanides are hydrolysed by acids or alkalis to the corresponding acid via the intermediate formation of an amide.

Example:

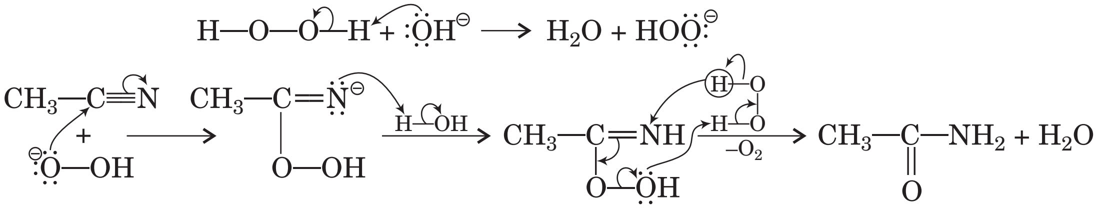
$$NH_3 + \underset{\text{Acetate ion}}{CH_3CO_2^{\ominus}} \xleftarrow[(aq.\ NaOH)]{OH^{\ominus}/H_2O,\ \Delta} CH_3CN \xrightarrow[(dil.\ HCl)]{H_3O^{\oplus}/\Delta} \underset{\text{Acetic acid}}{CH_3CO_2H} + NH_4^{\oplus}$$

2. Alkyl cyanides react with alkaline H_2O_2 to yield amides.

Example:

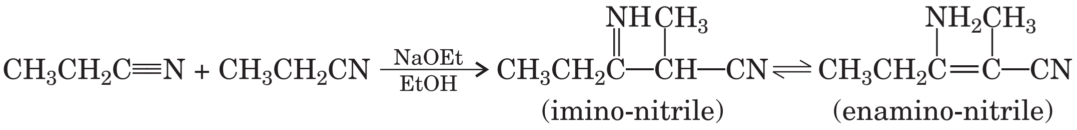
$$CH_3CN \xrightarrow{H_2O_2/OH^{\ominus}} CH_3CONH_2 + O_2 + H_2O$$

Mechanism of the reaction:


H—O—O—H + :ÖH⊖ ⟶ H₂O + HOÖ:⊖
CH₃—C≡N + ⊖:Ö—OH ⟶ CH₃—C=N̈⊖ | O—OH
H—OH
CH₃—C=NH | O—ÖH
H—O | H—O
–O₂
CH₃—C—NH₂ + H₂O ‖ O

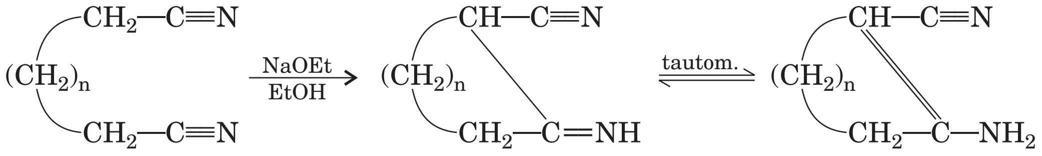
3. Thorpe nitrile condensation Base-catalyzed condensation between two cyanide molecules, where the α-carbon of one molecule is added to the cyano carbon of the other, is called *Thorpe nitrile condensation* or simply *Thorpe reaction*. The initially formed imino-nitrile is readily tautomerized into the more stable enaminino-nitrile.

Example:



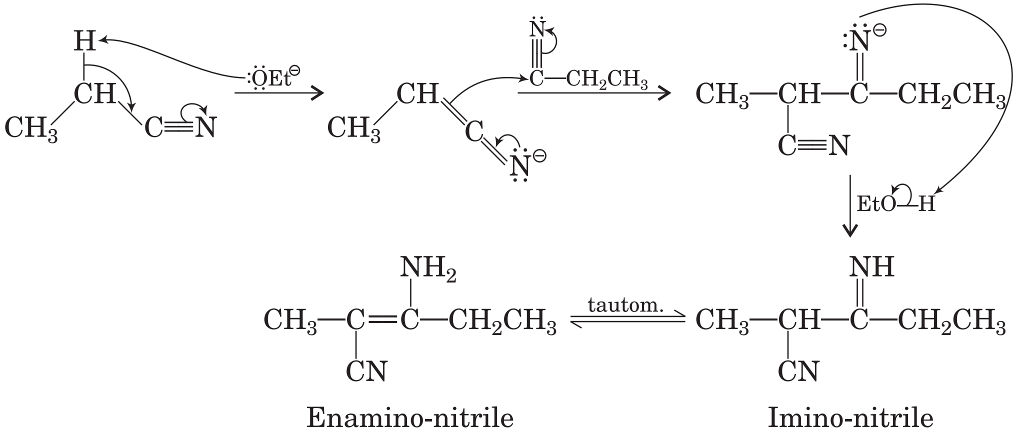
$$CH_3CH_2C\equiv N + CH_3CH_2CN \xrightarrow[EtOH]{NaOEt} CH_3CH_2\overset{\overset{NH}{\|}}{C}-\overset{\overset{CH_3}{|}}{CH}-CN \rightleftharpoons CH_3CH_2\overset{\overset{NH_2}{|}}{C}=\overset{\overset{CH_3}{|}}{C}-CN$$

When the reaction is carried out intramolecularly, the method is called the *Thorpe-Ziegler reaction*. This is a useful method for preparing large rings (5- to 8-membered).



n = 2 to 5

Mechanism of the reaction:



Alkyl isonitrile or isocyanides

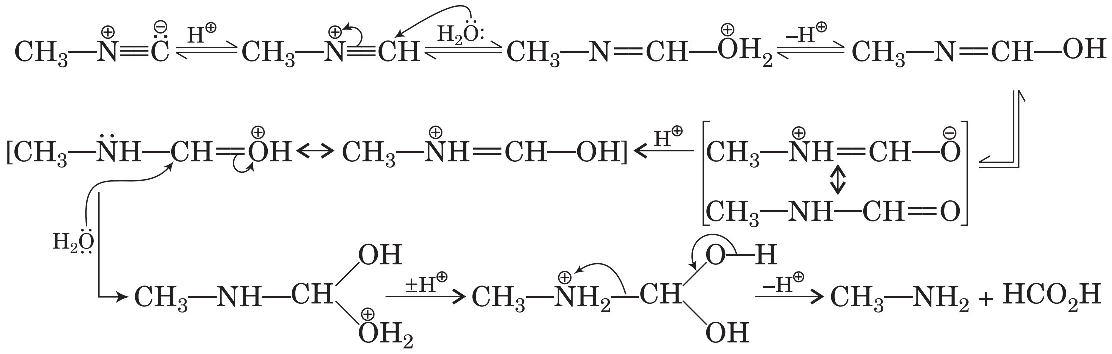
1. Hydrolysis Alkyl isocyanides undergo hydrolysis only by dilute acid to yield primary amines and formic acid. Dilute alkali has no action on alkyl isocyanides.

Example:

$$CH_3{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{C}: \xrightarrow{\text{dil. HCl}} CH_3NH_2 + HCO_2H$$

Methyl isocyanide — Methylamine (a 1° amine) — Formic acid

Mechanism of the reaction:



2. Reduction Isocyanides are reduced catalytically to 2° methyl-amines.

Example:

$$CH_3{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{C}: \xrightarrow{H_2/Pt} CH_3NHCH_3$$

Methyl isocyanide — Dimethylamine

SOLVED PROBLEMS

1. **Explain why alkyl isocyanides do not undergo hydrolysis by alkali.**

Solution The carbon atom of the –NC group is an alkyl isocyanide bears a negative charge, and so, it cannot coordinate with the $OH^{\ominus}$ ion. Again, the outer shell of the tetracovalent positively charged N atom is saturated, and as a consequence, it has no capacity to accommodate two more electrons in that shell. For these reasons, alkyl isocyanides do not undergo hydrolysis by alkali.

2. **How would you distinguish between methyl cyanide and methyl isocyanide?**

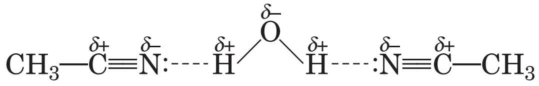
Solution Methyl cyanide undergoes alkaline hydrolysis followed by acidification to give acetic acid. When acetic acid is treated with anhydrous ethanol in the presence of a small amount of conc. H_2SO_4, the ester ethyl acetate having characteristic sweet odour is obtained. Methyl isocyanide, on the other hand, does not undergo alkaline hydrolysis.

$$\underset{\text{Methyl cyanide}}{CH_3CN} \xrightarrow[H_2O]{NaOH} CH_3CO_2Na \xrightarrow{H_3O^{\oplus}} CH_3COOH \xrightleftharpoons{EtOH/H^{\oplus}} \underset{\substack{\text{Ethyl acelate}\\ \text{(sweet smell)}}}{CH_3COOEt}$$

$$CH_3NC \xrightarrow[H_2O]{NaOH} \text{No reaction}$$

3. Between methyl cyanide and methyl isocyanide which one is more soluble in water and why?

Solution The N-atom in the molecule of methyl cyanide ($CH_3-\overset{\delta+}{C}\equiv\overset{\delta-}{N}:$) is partially negatively charged and it has a lone pair of electrons with which it can form hydrogen bond with water molecule. For this reason, methyl cyanide shows sufficient solubility in water.



(intermolecular H-bond)

On the other hand, the N-atom in the molecule of methyl isocyanide ($CH_3-\overset{\delta+}{\ddot{N}}=\overset{\delta-}{C}:$] becomes partially positively charged and hence, it cannot use its unshared pair of electrons to form H-bond with water molecule. So, this compound is almost insoluble in water.

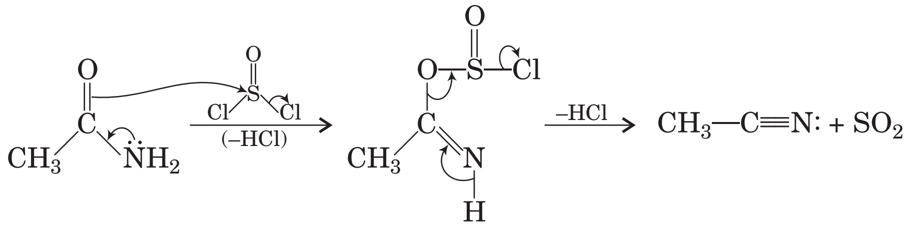
4. Suggest a mechanism for each of the following reactions:

(a) $\mathbf{CH_3CONH_2 \xrightarrow{SOCl_2} CH_3C\equiv N}$

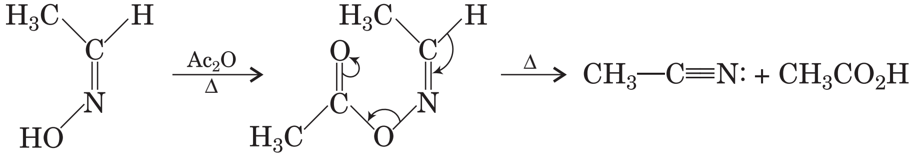
(b) $\mathbf{CH_3CH{=}NOH \xrightarrow[\Delta]{Al_2O} CH_3C\equiv N}$

Solution

(a)

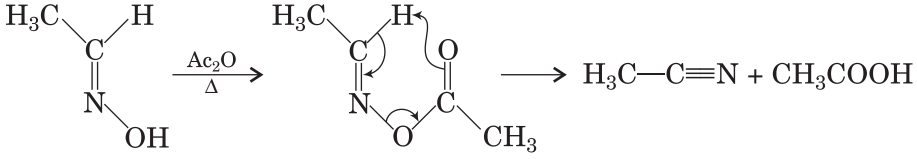


(b)



(*Z*)-Oxime

or



(*E*)-Oxime

Study Problems

1. Out of methyl cyanide and methylamine which one is more basic and why?
2. Can acetonitrile (CH_3CN) exhibits acidic property? Explain your answer.
3. Why does an isocyanide behave as a reducing agent? Explain with an example.

1.6 DIAZONIUM SALTS AND THEIR RELATED COMPOUNDS

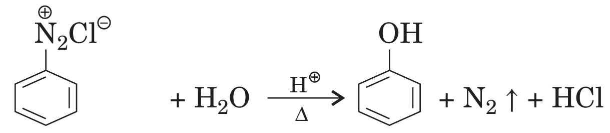
1.6.1 Reactions

The reactions of diazonium salts are of three types. These are: 1. substitution reactions, 2. reduction reactions and 3. coupling reactions.

1. Substitution reactions These reactions involve replacement of diazonium group $(-\overset{\oplus}{N}_2)$ by any other group or atom, with the evolution of N_2 gas.

1A. Substitution by hydroxyl (–OH) group When a diazonium salt solution is slowly added to boiling water acidified with dilute H_2SO_4 or when highly acidified diazonium salt solution is heated, the salt undergoes hydrolysis along with the replacement of the diazonium group $(-\overset{\oplus}{N}_2)$, by a hydroxyl group (–OH).

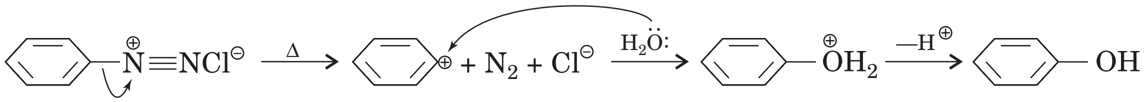
Example:



Benzenediazonium chloride

Phenol

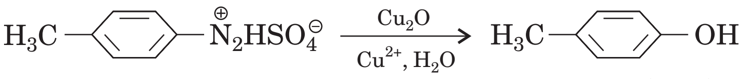
Mechanism of the reaction: It is an aromatic S_N1 reaction. At a higher temperature, benzenediazonium cations becomes destabilised and decomposes readily to liberate N_2 gas. The phenyl cation, thus, obtained combines with water to give phenol.



Phenol

The diazonium group can be replaced by a hydroxyl group by adding cuprous oxide to a dilute solution of the diazonium salt containing a large excess of cupric nitrate.

Example:



p-Toluenediazonium hydrogen sulphate

p-Cresol (93%)

This variation of the Sandmeyer reaction is much simpler and safer method than the older method for phenol preparation, which requires heating the diazonium salt with concentrated aqueous acid.

1B. Substitution by hydrogen atom When a diazonium salt is treated with hypophosphorous acid (H_3PO_2), it undergoes reduction and the diazonium group ($-\overset{\oplus}{N}_2$) is replaced by hydrogen.

Example:

$$C_6H_5\overset{\oplus}{N}_2Cl^{\ominus} + H_3PO_2 + H_2O \xrightarrow{0°C} C_6H_6 + H_3PO_3 + HCl + N_2\uparrow$$

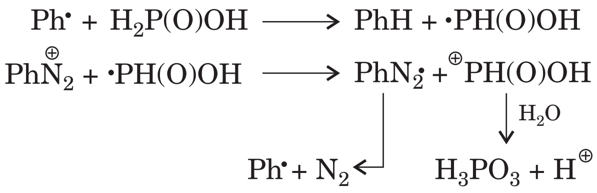
The $-NH_2$ group attached to an aromatic ring may, thus, be removed and the process is known as *deamination*.

Mechanism of the reaction: A highly favoured mechanism for this reaction involves a free-radical chain:

Chain initiation

$$Ph\overset{\oplus}{N}_2Cl^{\ominus} + H_2P(O)OH \longrightarrow HCl + Ph{-}N{=}N{-}PH(O)OH \longrightarrow Ph\cdot + N_2 + \cdot PH(O)OH$$

Chain propagation



$$Ph^{\bullet} + H_2P(O)OH \longrightarrow PhH + {}^{\bullet}PH(O)OH$$

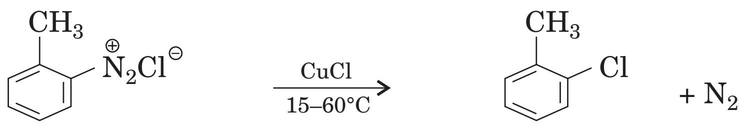
$$Ph\overset{\oplus}{N}_2 + {}^{\bullet}PH(O)OH \longrightarrow PhN_2^{\bullet} + {}^{\oplus}PH(O)OH$$

$$PhN_2^{\bullet} \longrightarrow Ph^{\bullet} + N_2 \qquad {}^{\oplus}PH(O)OH \xrightarrow{H_2O} H_3PO_3 + H^{\oplus}$$

$NaBH_4$ and ethanol can also be used for the replacement of the diazonium group by hydrogen.

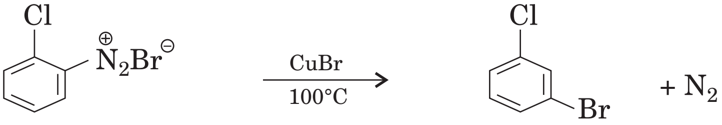
1C. Substitution by –Cl, –Br, or –CN The Sandmeyer reaction: Cuprous salts have a special affinity for diazonium salts. Arene diazonium salts react with cuprous chloride, cuprous bromide, and cuprous cyanide to give aryl chlorides, aryl bromides, and aryl cyanides, respectively. These reactions are known generally as *Sandmeyer reactions*. These reactions may also be carried out with CuCl/HCl, CuBr/HBr or CuCN/aq. KCN or Cu powder/aq. KCN.

Examples:



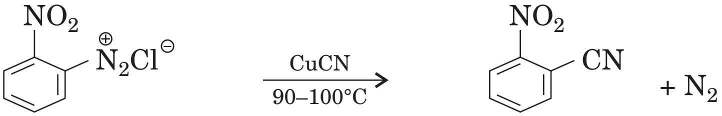
o-Methylbenzenediazonium chloride

o-Chlorotoluene



m-Chlorobenzenediazonium bromide

m-Bromochlorobenzene (70%)



o-Nitrobenzenediazonium

o-Nitrobenzonitrile (65%)

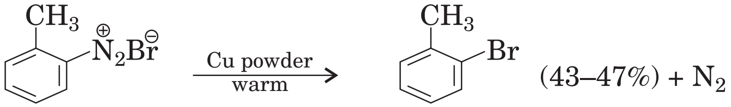
Mechanism of the reaction: The mechanism of the reaction is uncertain. A possibility is as follows:

$$\mathrm{CuCl} + :\ddot{\underset{\cdot\cdot}{\mathrm{Cl}}}:^{\ominus} \longrightarrow \mathrm{CuCl}_2^{\ominus}$$

$$\mathrm{ArN}_2^{\oplus} + \mathrm{Cl{-}}\overset{\ominus}{\mathrm{Cu}}\mathrm{{-}Cl} \xrightarrow{\text{slow}} \mathrm{N}_2 + \mathrm{Ar}\cdot + \mathrm{Cl{-}Cu{-}Cl} \xrightarrow{\text{fast}} \mathrm{ArCl} + \mathrm{CuCl}$$

Replacement of the diazonium group $(-\overset{\oplus}{N}_2)$ by halogen may be effected by warming the diazonium salt solution in the presence of Cu powder. The reaction is known as the *Gattermann reaction*.

Example:

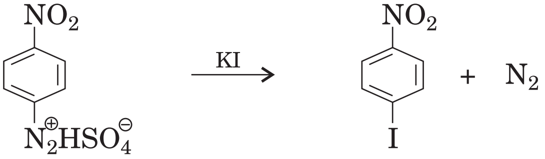


o-Methyl benzenediazonium bromide

o-Bromotoluene

1D. Substitution by –I Arenediazonium salts react with potassium iodide to give products in which the diazonium group has been replaced by –I.

Example:

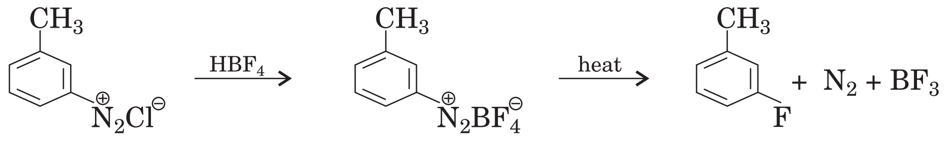


p-Nitrobenzenediazonium hydrogen sulphate

p-Iodonitrobenzene (81%)

1E. Substitution by –F When an arenediazonium salt is treated with fluoroboric acid (HBF_4), the diazonium fluoroborate precipitates out of the solution. The precipitated salt is then filtered, dried and heated until decomposition occurs. An aryl fluoride is produced.

Example:

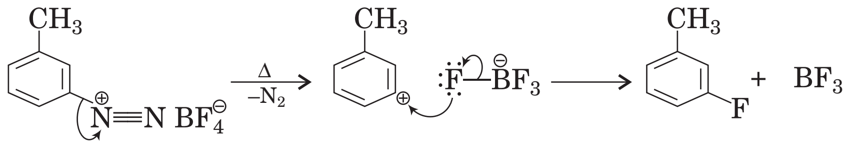


m-Methyl-benzenediazonium chloride

m-Methyl-benzenediazonium fluoroborate

m-Fluorotoluene (69%)

Mechanism of the reaction:



1F. Substitution by an aryl group This may be carried out by treating a diazonium hydrogen sulphate with ethanol and copper powder.

Example:

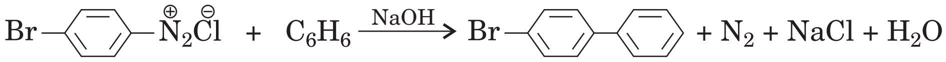
$$2\ C_6H_5\overset{\oplus}{N_2}\ \overset{\ominus}{HSO_4} \xrightarrow[\text{Cu}]{C_2H_5OH} C_6H_5C_6H_5 + 2N_2 + 2H_2SO_4$$

Benzenediazonium hydrogen sulphate

Biphenyl (25%)

Alternatively, a biaryl may be prepared by adding an aromatic compound to an alkaline solution of a diazonium salt.

Example:

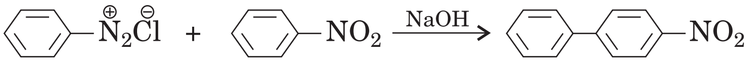


p-Bromobenzenediazonium chloride

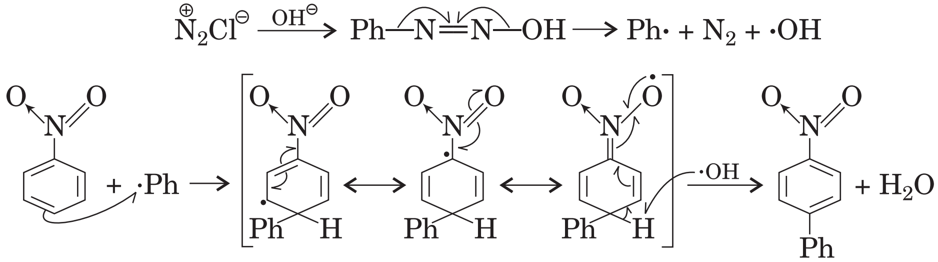
p-Bromobiphenyl (35%)

This method of preparation is known as the *Gomberg reaction*. It is to be noted that whatever is the nature of a substituent in the second component, *o*- or *p*-substitution always occurs predominantly.

Example:

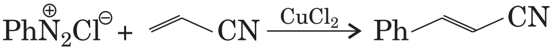


Mechanism of the reaction: the reaction takes place by a free-radical mechanism involving the steps as follows:

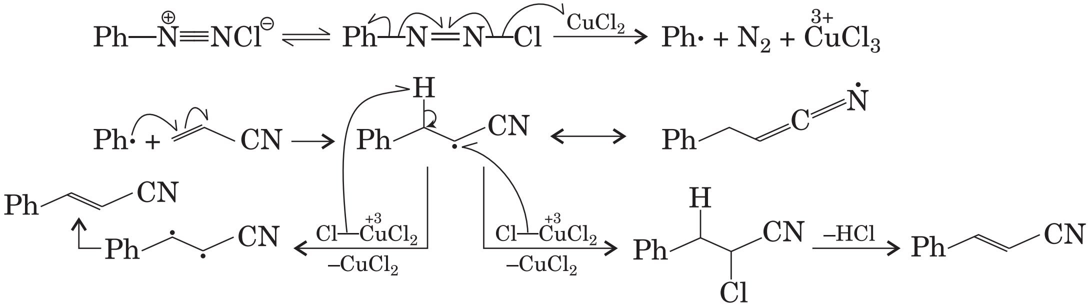


Meerwein arylation reaction: Olefins activated by an electron-attracting group (e.g., >C=O —C≡N, etc.) can be arylated by treatment with a diazonium salt and cupric chloride. This is called the *Meerwein arylation reaction*.

Example:

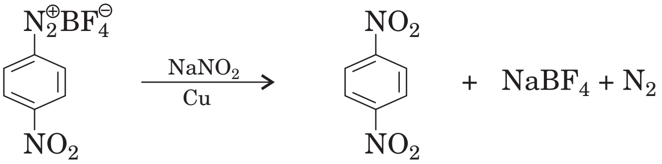


Mechanism of the reaction: A radical mechanism has been proposed for this reaction.



1G. Substitution by a –NO$_2$ group When a diazonium fluoroborate is decomposed with aqueous sodium nitrite containing copper powder, the diazonium group undergoes substitution by a –NO$_2$ group.

Example:



p-Nitrobenzenediazonium fluoroborate

p-Dinitrobenzene (67–82%)

2. Reduction reactions

2A. Reduction by SnCl$_2$/HCl or Sodium Sulphite When diazonium salts are reduced by SnCl$_2$/HCl or Na$_2$SO$_3$, arylhydrazine hydrochlorides are obtained.

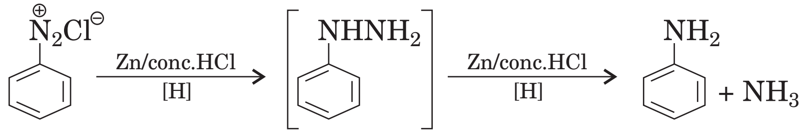
Examples:

$$\mathrm{Ph\overset{\oplus}{N}_2\overset{\ominus}{Cl} + 2\,Na_2SO_3 + 2\,H_2O \xrightarrow{[H]} PhNHNH_2 + 2\,Na_2SO_4 + HCl}$$

$$\underset{\text{Benzenediazonium chloride}}{\mathrm{Ph\overset{\oplus}{N}_2\overset{\ominus}{Cl}}} \xrightarrow[\text{[H]}]{\mathrm{SnCl_2/HCl}} \underset{\text{Phenylhydrazine hydrochloride}}{\mathrm{PhNHNH_2{\cdot}HCl}}$$

2B. Reduction by Zn/conc. HCl When the reduction of a diazonium salt is carried out with Zn/conc. HCl, the N–N bond cleavage with the formation of an aromatic 1° amine and NH_3 occurs.

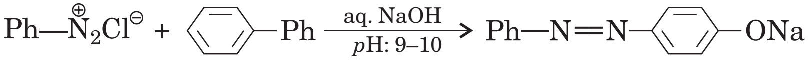
Example:



Benzenediazonium chloride | Phenylhydrazine | Aniline

3. Coupling reactions Diazonium salts readily combine with phenols, naphthols and aromatic amines to form highly coloured (orange, red or yellow) azo compounds. These reactions in which the N atoms are retained are called *coupling reactions*. Phenols couple readily in weakly alkaline solution. Aromatic amines undergo the coupling reaction in weakly acidic solution.

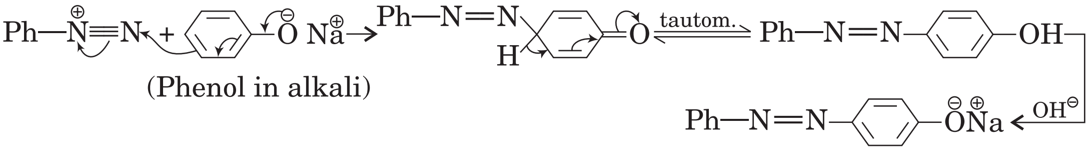
3A. Coupling reaction with phenol When cold solution of benzenediazonium chloride is added to the cold alkaline solution of phenol, coupling reaction occurs and an orange azo compound called *p*-hydroxyazobenzene (salt) is produced.



p-Hydroxyazobenzene
(sodium salt) (orange)

Because of steric strain, coupling preferentially occurs in the *p*-position of the hydroxyl group. But if this position is blocked, then *o*-coupling occurs.

Mechanism of the reaction: This is an electrophilic substitution reaction.

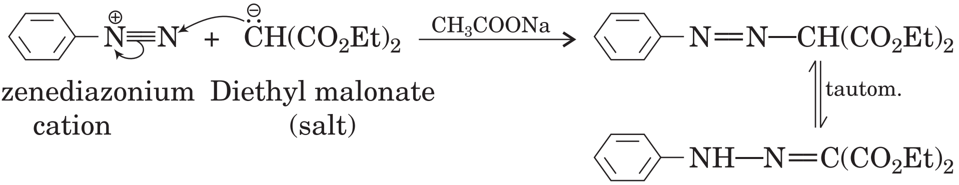


Ph—$\overset{\oplus}{N}$≡N +
$\overset{\ominus}{O}$ $\overset{\oplus}{Na}$
(Phenol in alkali)
Ph—N═N
H
O
tautom.
Ph—N═N—
OH
$OH^{\ominus}$
Ph—N═N—
$\overset{\ominus}{O}\overset{\oplus}{Na}$

The coupling reaction with *β*-naphthol is already discussed.

3B. Japp–Klingermann reaction Coupling also occurs (in CH_3COONa buffered solution) with compounds containing an active methylene group, e.g., diethyl malonate, ethyl acetoacetate, etc. to give the phenyl hydrazone (formed by the tautomerisation of the azo-compound to the more thermodynamically stable hydrazone).

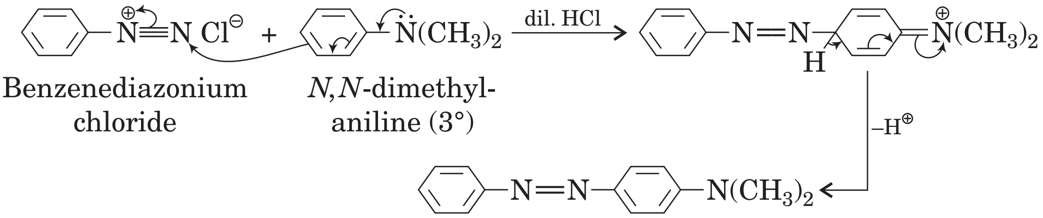
Example:



This coupling reaction is often used to detect the presence of enols and is then referred to as the *Japp-Klingermann reaction*.

3C. Coupling reaction with tertiary amine In neutral or weakly acidic solution, *N*, *N*-dimethylaniline undergoes coupling reaction with benzenediazonium chloride. The coupling occurs at the *C*-atom (*C*-coupling) of the ring to form *p*-(*N*, *N*-dimethylamino) azobenzene. Due to lack of hydrogen on nitrogen, *N*-coupling does not take place.

Example:

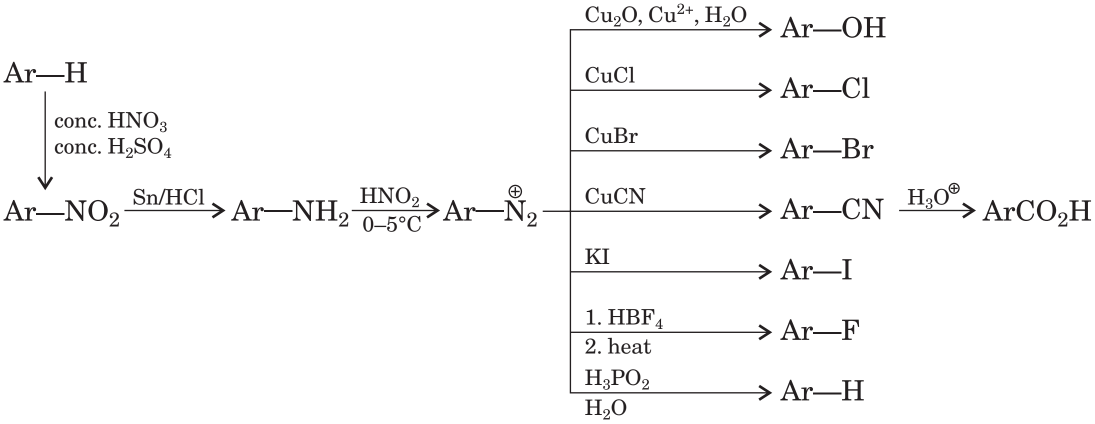


p-(*N*,*N*-dimethylamino) azobenzene
(Butter Yellow)

It is to be noted that coupling with primary and secondary amine occurs mainly at the nitrogen atom, i.e., *N*-coupling occurs.

1.6.2 Syntheses Using Diazonium Salts

Replacement of the diazonium group ($-\overset{\oplus}{N}_2$) is the best general way of introducing F, Cl, Br, I, CN, OH and H into an aromatic ring. Diazonium salts are valuable in synthesis not only because they react to form so many classes of compounds but also because they can be easily prepared from nearly all primary aromatic amines. The 1° amines form which diazonium compounds are prepared are readily obtained from the corresponding nitro compounds, which are prepared by direct nitration. Therefore, the diazonium salts are the most important link in the sequence given below:



Most arenediazonium salts are unstable at temperatures above 5–10°C, and many explode when dry. Fortunately, however, most of the displacement reactions of diazonium salts can be carried out without isolating them. The replacement accompanied by the evolution of N_2 gas occurs when the reagent (CuCl, Cu Br, KI, etc.) is simply added to the mixture and then the solution is warmed gently.

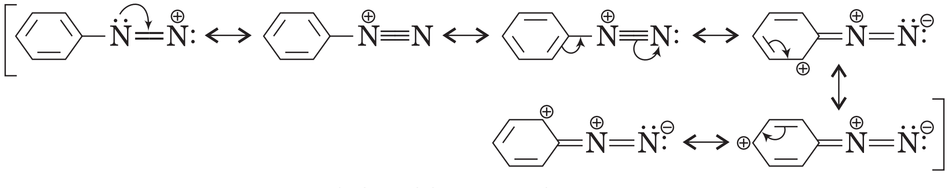
Hydrolysis of nitriles yields carboxylic acids. Therefore, the synthesis of nitriles from diazonium salts provides us with an excellent route from nitro compounds to carboxylic acids. The procedure of preparing carboxylic acids is more generally useful than either carbonation of a Grignard reagent (reaction with CO_2) or oxidation of side chains. The reasons are as follows: (i) there are many groups that interfere with the preparation and use of the Grignard reagent, (ii) the nitro group can be introduced into a molecule more readily than an alkyl side chain; also, the conversion of a side chain into a carboxyl group cannot be carried out on molecules that contain other groups sensitive to oxidation.

The coupling of diazonium salts with phenols and aromatic amines produces azo compounds, which are of tremendous importance to the dye industry.

SOLVED PROBLEMS

1. $C_6H_5\overset{\oplus}{N}_2$ is more stable than $CH_3\overset{\oplus}{N}_2$. Explain.

Solution The diazonium cation from aniline, i.e., $C_6H_5\overset{\oplus}{N}_2$, is stabilized by resonance but that from methylamine, i.e., $CH_3\overset{\oplus}{N}_2$, is not. For this reason, $C_6H_5\overset{\oplus}{N}_2$ is relatively more stable than $CH_3\overset{\oplus}{N}_2$.



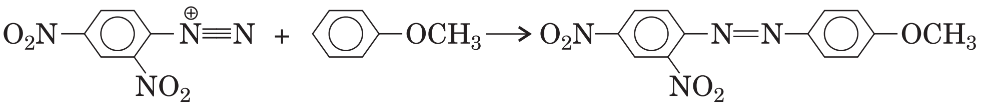
Resonance stabilized benzenediazonium cation

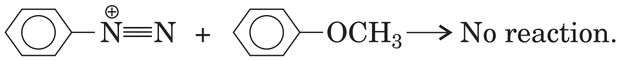
2. **Predict whether $Ph\overset{\oplus}{N}_2$ couples with $PhNMe_2$, PhOH or $PhCH_3$. Give your reasoning.**

Solution $Ar\overset{\oplus}{N}_2$ is a weak electrophile that undergo diazo coupling reaction only with rings containing strongly activating groups like –OH (in alkaline medium $-O^{\ominus}$), $-NR_2$, etc. and not weakly activating group –R. Therefore, $Ph\overset{\oplus}{N}_2$ couples with $PhNMe_2$ and PhOH but not with $PhCH_3$.

3. **2, 4-$(O_2N)_2C_6H_3\overset{\oplus}{N}_2$ couples with anisole ($PhOCH_3$) but $Ph\overset{\oplus}{N}_2$ does not. Explain.**

Solution In anisole, the ring is not sufficiently activated by $-OCH_3$ to react with the weakly electrophilic $Ph\overset{\oplus}{N}_2$. The electron-withdrawing nitro groups make the diazonium ion less stable and thus more reactive than $Ph\overset{\oplus}{N}_2$. This explains why 2,4-$(O_2N)_2C_6H_3\overset{\oplus}{N}_2$ couples with anisole, but $Ph\overset{\oplus}{N}_2$ does not.





4. **(a) Explain why the following conditions are unsatisfactory for diazo coupling: (i) strong acid and (ii) strong base. (b) what conditions are used to disfavour coupling during diazotization of $ArNH_2$?**

Solution

(a) (i) In the presence of strong acid, $ArNH_2$ is converted to $Ar\overset{\oplus}{N}H_3$, whose ring is deactivated to coupling.

(ii) In the presence of strong base, $Ar\overset{\oplus}{N}_2$ becomes converted to a diazoic acid (Ar—N=N—OH) and then to a diazotate anion (Ar—N=N—$O^{\ominus}$). Neither the diazoic acid nor its anion couple.

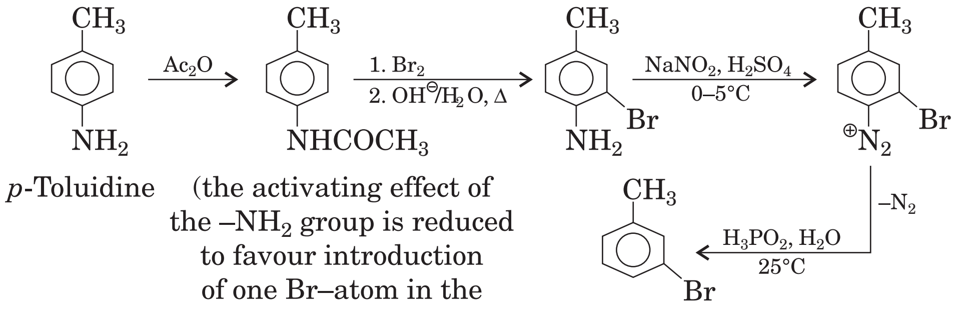
(b) During diazotization, it is necessary to avoid coupling of $Ar\overset{\oplus}{N}_2$ with the unreacted $ArNH_2$. If an excess of mineral acid is used, most of $ArNH_2$ becomes largely converted to $Ar\overset{\oplus}{N}H_3$, which does not couple. In a weakly acidic medium, the diazonium ion reacts with the free amine to form a diazoamino compound (Ar—N=N—NHAr).

5. **Replacement of the diazonium group by –H can be a useful reaction. Illustrate with examples.**

Solution An amino group can be introduced into an aromatic ring to influence the orientation of a subsequent reaction. Later the amino group can be removed by diazotizing it and treating the diazonium salt with H_3PO_2. Deamination by diazotizaton can also be used to protect a particular position.

Examples:

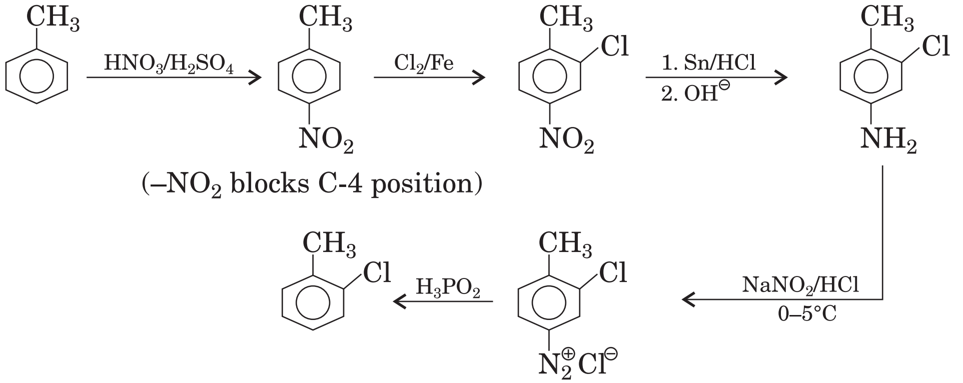
(i) **Synthesis of *m*-bromotoluene**



p-Toluidine (the activating effect of the –NH_2 group is reduced to favour introduction of one Br–atom in the next step.)

m-Bromotoluene

(ii) **Synthesis of *o*-chlorotoluene**

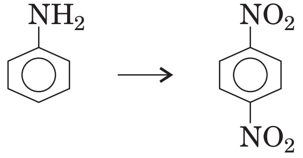


(–NO_2 blocks C-4 position)

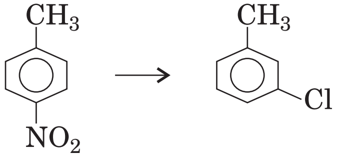
The *para* position is blocked by –NO_2, and so, chlorination occurs only at *ortho* to –CH_3.

6. **How would you carry out the following transformations:**

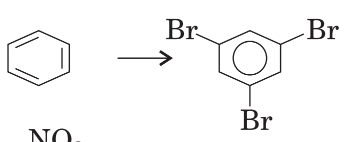
(a)



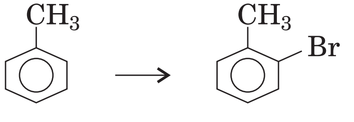
(b)



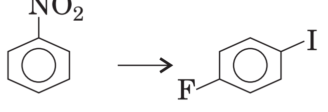
(c)



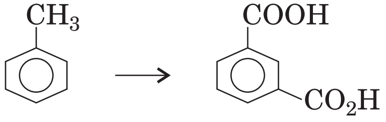
(d)



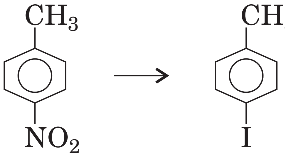
(e)



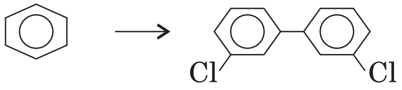
(f)



(g)

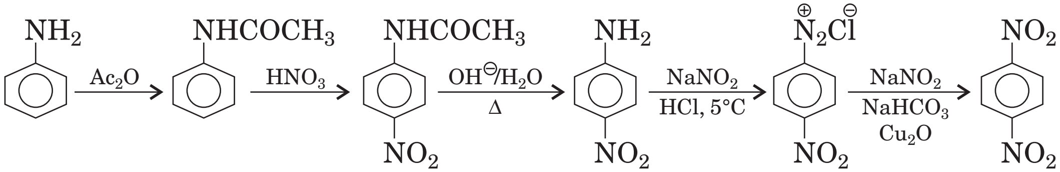


(h)

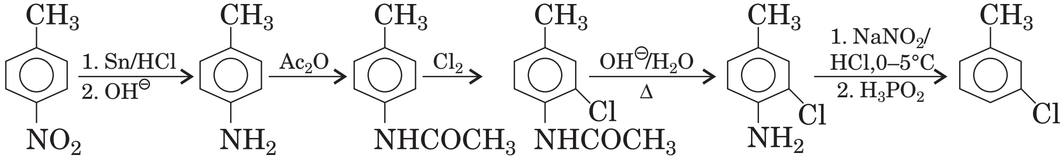


Solution

(a)



(b)



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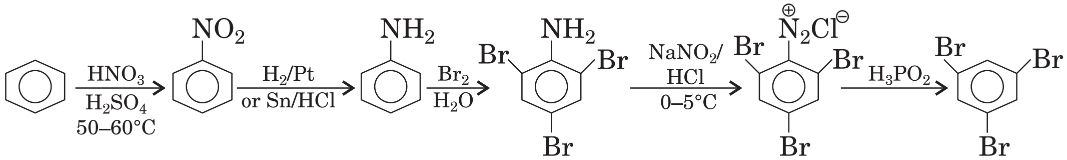

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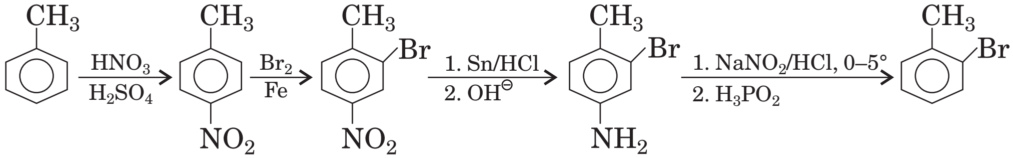

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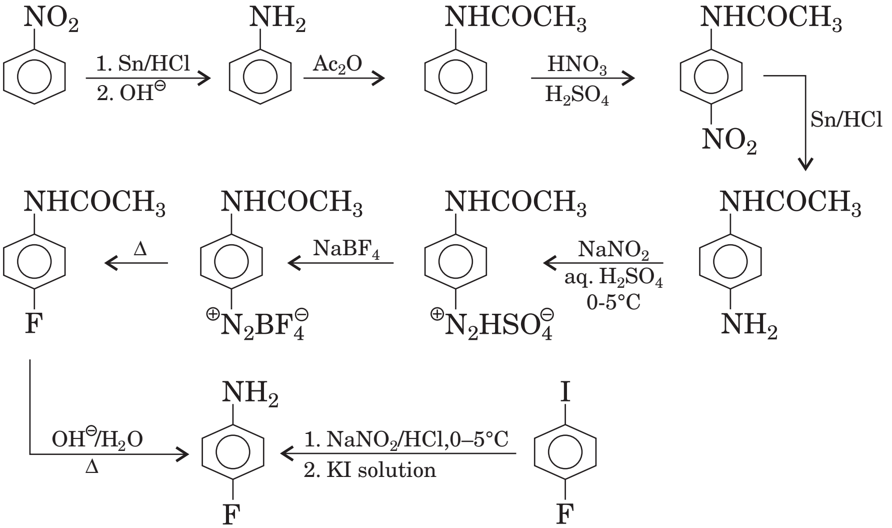

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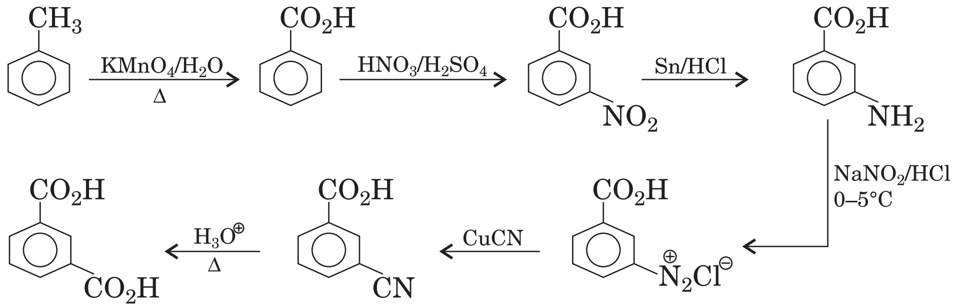

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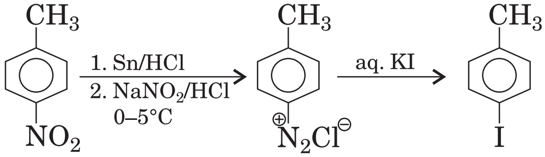

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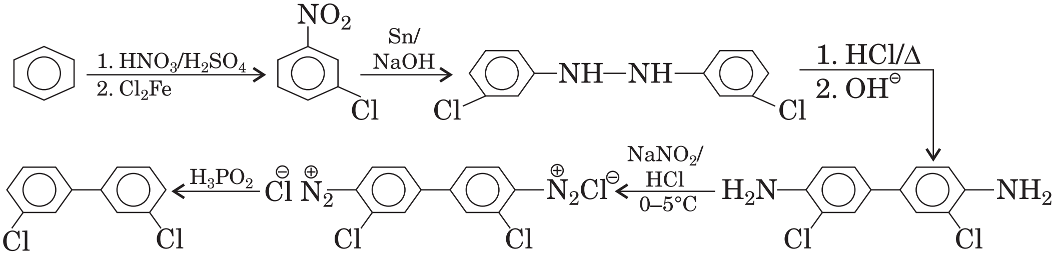
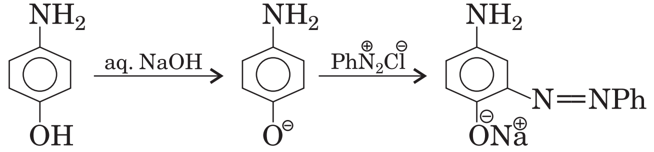
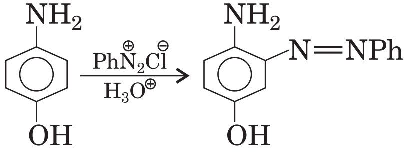


7. $Ph\overset{\oplus}{N}_2Cl^{\ominus}$ is allowed to couple with *p*-$H_2NC_6H_4OH$ under (a) acidic condition and (b) basic condition. Predict the products and explain.

Solution When $Ph\overset{\oplus}{N}_2Cl^{\ominus}$ is allowed to couple with *p*-aminophenol, two isomeric *C*-coupled products are formed. The reactions are given below. These are electrophilic substitutions where the diazonium cation in the electrophile.



(coupling under basic conditions)



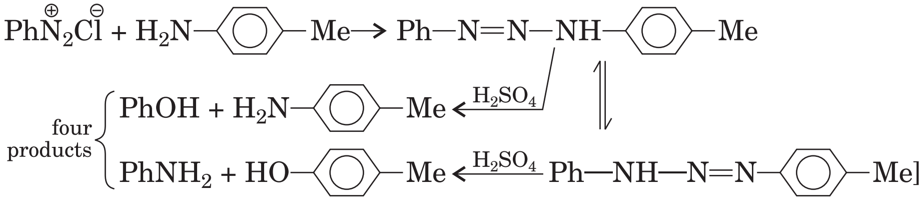
(Coupling under acidic conditions)

This difference in reactions can be explained on the basis of the orienting strength of the two groups in acidic and basic conditions. Under basic conditions, the resulting phenoxide ion ($–O^{\ominus}$) is more reactive than the $–NH_2$ group. As a result, coupling occurs *ortho* to the –OH group. Under acidic conditions, phonolic –OH does not dissociate and then the lone pair of electrons on the less electronegative and more polarizable N atom of the $–NH_2$ group is relatively more reactive compared to the lone pair of electrons on the more electronegative O atom of the –OH group. As a consequence, coupling occurs *ortho* to the $–NH_2$ group.

Study Problems

1. Diazonium salts are not generally separated in solid state—Why?
2. Give the mechanism of diazotization of aniline.
3. What is coupling reaction? Give an example.
4. Explain why benzenediazonium chloride couples with aniline to give both *C*- and *N*-coupled products.
5. What happens when (a) *o*-aminophenol and (b) *o*-phenylenediamine are separately diazotized?
6. Give examples of two reactions of diazonium salts in each, where (a) N_2 gas is eliminated, and (b) nitrogen atoms are retained in the product.
7. *p*-Toluidine reacts with benzenediazonium chloride to form a compound which, on boiling with H_2SO_4, gives four products (excluding nitrogen). Discuss.

[**Hint:**



8. Discuss the mechanism of coupling reaction and mention the effect of acidity or alkalinity of the medium of coupling.
9. How would you carry out the following transformations:
   (a) $C_6H_5CHO \longrightarrow m\text{-}ClC_6H_4CHO$
   (b) $C_6H_6 \longrightarrow m\text{-}FC_6H_4NO_2$
   (c) $PhMe \longrightarrow 3\text{-}Br\text{-}4\text{-}NO_2\text{-toluene}$
   (d) *o*-Nitrotoluene ⟶ *o*-Cresol
   (e) $C_6H_6 \longrightarrow$ *m*-Difluorobenzene
10. Suggest a mechanism for each of the following reactions:

(a) $Ph\overset{\oplus}{N}_2Cl^{\ominus} + CH_2(CN)CO_2Et \xrightarrow{NaOAc} PhNHN{=}C(CN)CO_2Et$

(b) $Ph\overset{\oplus}{N}_2BF_4^{\ominus} + PhNO_2 \xrightarrow{\Delta} m\text{-}O_2NC_6H_4Ph$

(c) $p\text{-}ClC_6H_4\overset{\oplus}{N}_2Cl^{\ominus} + CH_2{=}CHCHO \xrightarrow{Cu^{2+}} p\text{-}ClC_6H_4CH_2CHClCHO$

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2. Gilchrist and Rees, *Carbenes, Nitrenes and Aryns*, Nelson (1969).
3. Cook, A. G., *Enamines: Synthesis, Structure, and Reactions*; Wiley: New York, 1969.
4. Miller, I. T. and Springall, H. D. *Sidgwick's Organic Chemistry of Nitrogen*, 3rd ed.; Clarendon: Oxford, 1966.
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Organometallic Compounds

2

Chapter Outline

Introduction

2.1 Organometallic Nomenclature

2.2 Organomagnesium Compounds or Grignard Reagents

- 2.2.1 Preparation of Grignard Reagents
- 2.2.2 Reactions of Grignard Reagents
- 2.2.3 Limitations in the Use of Grignard Synthesis

2.3 Organolithium Compounds

- 2.3.1 Preparation of Organolithium Compounds
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2.4 Organocuprates or Gilman Reagent

- 2.4.1 Preparation of Lithium Dialkylcuprates (Gilman Reagents)
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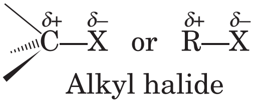
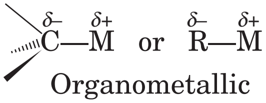
- 2.5.2 Reactions of Organozinc Compounds including Reformatsky and Simmon-Smith reactions

INTRODUCTION

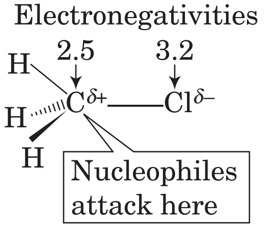
Compounds containing carbon–metal bonds are called *organometallic compounds*. When carbon is bonded to a more electronegative element like oxygen or chlorine, the electron distribution in the bond is polarized so that carbon is slightly positive and the more electronegative atom is slightly negative. Conversely, when carbon is bonded to a less electronegative element like a metal, the bonding electrons are more strongly attracted towards carbon. Electronegativity values for carbon and some common metals are C(2.5), Li(1.0), Mg(1.3) Zn(1.6) and Cu(1.8).

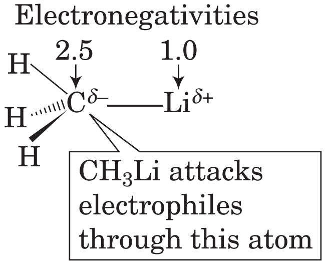


Alkyl halide
[X (Cl, Br, etc.) is more
electronegative than
carbon]



Organometallic
compound
[M (Li, Mg, etc.) is less
electronegative than carbon]





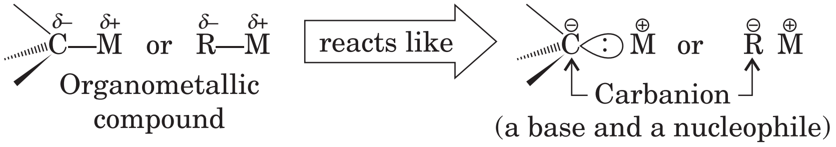
The ionic character of the C—M bond depends on the nature of the metal, e.g., the order of ionic character is K > Na > Li > Mg > Al > Zn > Cd > Cu, Hg. Some of the carbon—metal bonds are essentially ionic (e.g., the carbon—sodium, and carbon—potassium bonds in $\overset{\oplus}{Na}\,\overset{\ominus}{C}\equiv CH$ and $K^{\oplus}\,\overset{\ominus}{C}\equiv CH$, respectively) and some of the carbon—metal bonds are polar covalent (e.g., bonds like $\overset{\delta-}{C}—\overset{\delta+}{Li}$, $\overset{\delta-}{C}—\overset{\delta+}{Mg}$, $\overset{\delta-}{C}—\overset{\delta+}{Zn}$, etc.). Lithium, magnesium and copper are the most commonly used metals in organometallic compounds. General formulas of the three common organometallic compounds, where R is an alkyl, aryl, allyl or benzyl groups, are shown below:

R—Li	R—MgX	$R_2\overset{\ominus}{Cu}\overset{\oplus}{Li}$
Organolithium compounds (e.g., CH_3—Li)	Organomagnesium compounds or Grignard reagents (e.g., CH_3—MgI)	Organocopper compounds or organocuprates or Gilman reagents (e.g., $Me_2\overset{\ominus}{Cu}\,\overset{\oplus}{Li}$)

Like sodium acetylide $(\overset{\oplus}{Na}\,\overset{\ominus}{C}\equiv CH)$, sodium methoxide $\overset{\oplus}{Na}\,\overset{\ominus}{O}Me$ is an ionic compound. However, like sodium acetylide, it is not an organometallic compound because the negative charge in sodium methoxide resides on oxygen. Similarly, lead tetraacetate, $Pb(OAc)_4$, is not an organometallic compound.

The more the carbon—metal (C—M) bond polar, the more the organometallic compound is reactive. Alkylsodium and alkylpotassium compounds are highly reactive and are among the most powerful bases. They react explosively with water and unstable in air. Organomercury and organolead compounds are much less reactive. They are often volatile, stable in air and soluble in nonpolar solvents. Because both Li and Mg are very electropositive metals, organolithium (RLi) and organomagnesium compounds (RMgX) contain very polar carbon—metal bonds and are, therefore, very reactive reagents. They are stable in ether solutions. Because of considerable polarity of the C—M bond in RLi and RMgX, the carbon atom bonded to metal acts as a source of carbanion and therefore acts as a strong base as well as a powerful nucleophile.

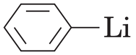
Organometallic compounds are synthetically very useful to organic chemists who need to make carbon—carbon bonds and this is because these compounds react as if they were free carbanions.



In this chapter, the preparation, properties and usefulness of some of the most common organometallic compounds are described.

2.1 ORGANOMETALLIC NOMENCLATURE

The IUPAC name of an organometallic compound starts with the name of the R group, followed by the name of the metal. For example,



Phenyllithium

$H_2C = CH\ Na$

Vinylsodium

Et_2Mg

Diethylmagnesium

When the metal bears an anionic ligand along with the R group, the ligand is named separately. For example,

EtMgBr	Et_2AlCl
Ethylmagnesium bromide	Diethylaluminium chloride

An exception to this nomenclature is the sodium salt of acetylene ($NaC{\equiv}CH$), which is normally referred to as sodium acetylide. However, both sodium acetylide and ethynylsodium are acceptable IUPAC names.

2.2 ORGANOMAGNESIUM COMPOUNDS OR GRIGNARD REAGENTS

Organomagnesium halides (general formula R—MgX, where R = alkyl or aryl group and X = Cl, Br or I) are the most important organometallic reagents in organic chemistry. They are discovered by the eminent French chemist Victor Grignard who received the coveted Nobel Prize for his discovery in 1912 and they are called Grignard reagents in his honour. The carbon—magnesium bond in them are highly polar bond, but the magnesium—halogen bond is basically ionic.

Examples:

CH_3MgI	C_6MgBr	$(CH_3)_2CHMgCl$
Methylmagnesium iodide	Phenylmagnesium bromide	Isopropylmagnesium chloride

2.2.1 Preparation of Grignard Reagents

2.2.1.1 Principle

A Grignard reagent is generally prepared by the reaction between clean and dry magnesium metal and dry alkyl or aryl halide in anhydrous alcohol-free ether. The organometallic halide produced in the reaction remain dissolved in ether. It is the ethereal solution of Grignard reagent, which is used for various chemical reactions.

$$\underset{\text{Alkyl or aryl halide}}{R—X} + Mg \xrightarrow[\text{Et}_2\text{O}]{\text{anhydrous}} \underset{\text{Grignard reagent}}{R—MgX}$$

Example:

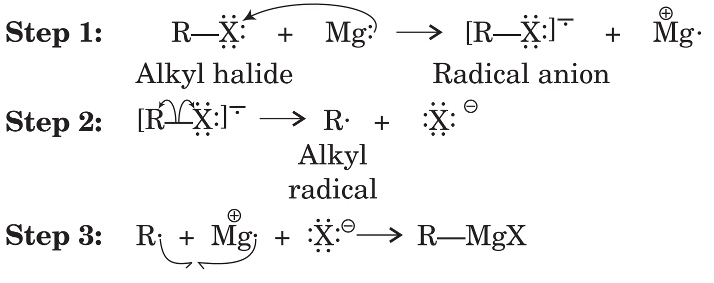
Methylmagnesium iodide is produced when methyl iodide is used as the alkyl iodide.

$$\underset{\text{Methyl iodide}}{CH_3I} + Mg \xrightarrow[\text{ether}]{\text{anhydrous}} \underset{\text{Methylmagnesium iodide}}{CH_3—MgI}$$

When an alkyl halide with positively polarized alkyl group $(\overset{\delta+}{R}—\overset{\delta-}{X})$ is converted to a Grignard reagent $(\overset{\delta-}{R}—\overset{\delta-}{MgX})$ by reacting with metallic magnesium, the alkyl group becomes negatively polarized. This reversal of polarity in the course of a reaction is generally referred to by the German term, *Umpolung*.

2.2.1.2 Mechanism of the Reaction

The formation of a Grignard reagent is similar to that of organolithium compounds except that each Mg atom participates in two separate one-electron transfer steps.



There is a change in oxidation state of the magnesium, from Mg(0) to Mg(II). The reaction is, therefore, known as an oxidative insertion or oxidative addition.

2.2.1.3 Some Important Informations Regarding the Preparation of Grignard Reagent

(i) In the preparation of Grignard reagent, the apparatus and the reagent must be perfectly dry and free from alcohol. The reaction atmosphere should be free from O_2, CO_2. Since R—MgX reacts like $R^{\ominus}$ (a strong base as well as a strong nucleophile), it readily reacts with water, alcohol, O_2 and CO_2 to produce the following products.

$$RMgX + H_2O \longrightarrow RH\uparrow + Mg(OH)X$$

$$RMgX + R'OH \longrightarrow RH\uparrow + Mg(OR')X$$

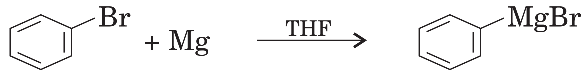
$$RMgX + O_2 \longrightarrow RO_2MgX$$

$$RMgX + CO_2 \longrightarrow RCOOMgX$$

(ii) Besides Et_2O, tetrahydrofuran (THF) is also used as a solvent in the preparation of Grignard reagents especially when the halogen atom is attached to an sp^2 carbon. For example:

$$CH_2 = CH - Br + Mg \xrightarrow{THF} CH_2 = CH - MgBr$$

Vinyl bromide Vinylmagnesium bromide



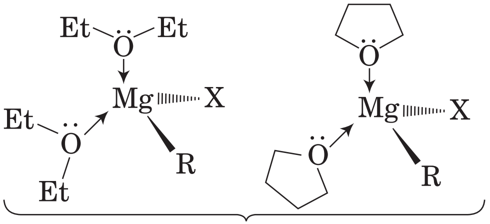
Bromobenzene Phenylmagnesium bromide

(iii) In the formation of Grignard reagent, the reactivity of alkyl halides follows the order: R—I > R—Br > R—Cl. Alkyl bromides are used most often because they react more readily than alkyl chlorides and are less expensive than alkyl iodides (alkylfluorides do not react).

(iv) In the case of particular halogen atom, the preparation of Grignard reagent becomes more and more different as the number of carbon atoms in the alkyl group increases. According to the nature of the alkyl group, the relative ease of formation of Grignard reagent follows the sequence:

$$CH_3—X > CH_3CH_2—X > (CH_3)_2CH—X > \cdots$$

(v) The solvent plays an important role in the formation of a Grignard reagent. The Mg atom in Grignard reagent has four valence electrons. It requires two pairs of electrons for the completion of electron octet. Oxygen atom of each ether molecule donates a pair of electrons to magnesium atom and as a consequence the octet of Mg becomes complete. Coordination of the solvent molecules with the Mg atom allows the Grignard reagent to dissolve in the solvent. X-ray diffraction studies have revealed that the two ether molecules are tightly bound to Mg in RMgX. The four groups are tetrahedrally arranged around magnesium.

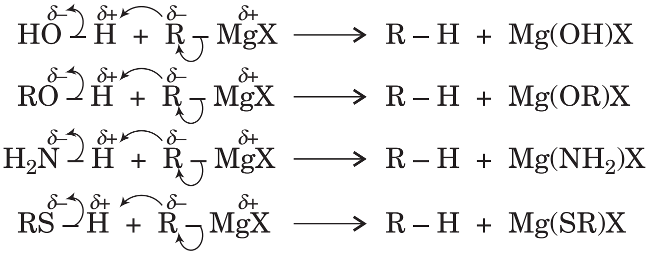


Dietherate compounds

2.2.2 Reactions of Grignard Reagents

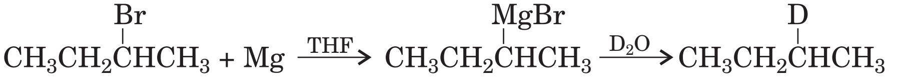
2.2.2.1 Reaction as a Base

Grignard reagents are very strong bases. They readily abstract a proton to produce a hydrocarbon from any compound that has an acidic hydrogen attached to more electronegative elements like oxygen, nitrogen, sulphur and even C_{sp}. In fact, Grignard reagents abstract proton from any substance more acidic than an alkane. For example:



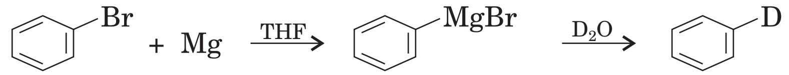
$$\overset{\delta-}{HO}-\overset{\delta+}{H} + \overset{\delta-}{R}-\overset{\delta+}{MgX} \longrightarrow R-H + Mg(OH)X$$
$$\overset{\delta-}{RO}-\overset{\delta+}{H} + \overset{\delta-}{R}-\overset{\delta+}{MgX} \longrightarrow R-H + Mg(OR)X$$
$$\overset{\delta-}{H_2N}-\overset{\delta+}{H} + \overset{\delta-}{R}-\overset{\delta+}{MgX} \longrightarrow R-H + Mg(NH_2)X$$
$$\overset{\delta-}{RS}-\overset{\delta+}{H} + \overset{\delta-}{R}-\overset{\delta+}{MgX} \longrightarrow R-H + Mg(SR)X$$

It is sometimes necessary in a synthesis to reduce an alkyl halide to a hydrocarbon. In such cases, converting the halide to the corresponding Grignard reagent and then adding water or alcohol as a proton source is a satisfactory procedure. Adding D_2O to a Grignard reagent is a commonly used method for introducing deuterium into a molecule. For example,



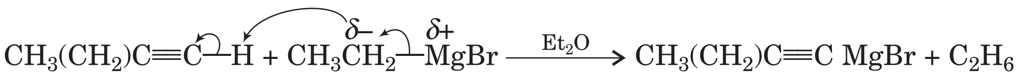
$$CH_3CH_2\overset{\overset{\displaystyle Br}{|}}{C}HCH_3 + Mg \xrightarrow{THF} CH_3CH_2\overset{\overset{\displaystyle MgBr}{|}}{C}HCH_3 \xrightarrow{D_2O} CH_3CH_2\overset{\overset{\displaystyle D}{|}}{C}HCH_3$$

2-Bromobutane | *sec*-Butylmagnesium bromide | 2-Deuteriobutane



Bromobenzene | Phenylmagnesium bromide | Deuteriobenzene

Acetylenic Grignard reagents of the type RC≡CMgBr are prepared, not from an acetylenic halide, but by an acid-base reaction in which a Grignard reagent abstracts a proton from a terminal alkyne in which hydrogen is attached to an *sp*-hybridized carbon and somewhat acidic. For example,

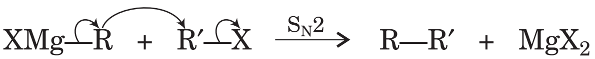


$$CH_3(CH_2)C{\equiv}C{-}H + \overset{\delta-}{CH_3CH_2}{-}\overset{\delta+}{MgBr} \xrightarrow{Et_2O} CH_3(CH_2)C{\equiv}C\,MgBr + C_2H_6$$

1-Hexyne Ethylmagnesium bromide 1-Hexnylmagnesium bromide Ethane

2.2.2.2 *Reaction as a Nucleophile*

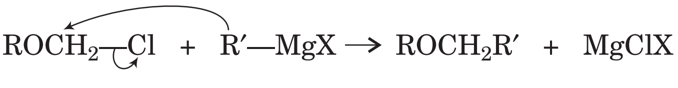
(a) Nucleophilic substitution reactions (Synthesis of alkanes, ethers and alcohols) Coupling between a Grignard reagent and alkyl halide containing a reactive halogen atom (e.g., Br) can be effected directly. The reaction is probably an S_N2 one.



$$XMg{-}R + R'{-}X \xrightarrow{S_N2} R{-}R' + MgX_2$$

Alkyl halide Alkane

The reaction actually occurs if R′ is allyl ($CH_2{=}CHCH_2{-}$), benzyl ($PhCH_2{-}$), etc. Another example of this type of reaction is the reaction between Grignard reagent and α-halogeno-ether. The reaction leads to a higher homologue of ether.



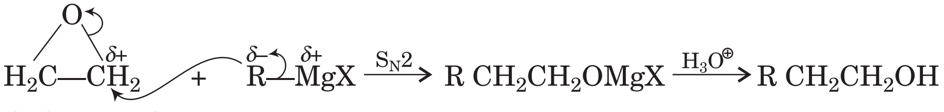
$$ROCH_2{-}Cl + R'{-}MgX \longrightarrow ROCH_2R' + MgClX$$

In fact, Grignard reagents are not good nucleophiles towards simple organic halides. If they were, the synthesis we use to generate these reagents in the presence of the starting organic halide would be quite ineffective, because hydrocarbons would be the major products. A good yield of R—R′ can be obtained for any R′ by using its tosyl ester (R′OTs).

A primary alcohol containing two carbon atoms more than the Grignard alkyl group can be prepared by adding one molecule of ethylene chlorohydrin to two molecules of Grignard reagent.

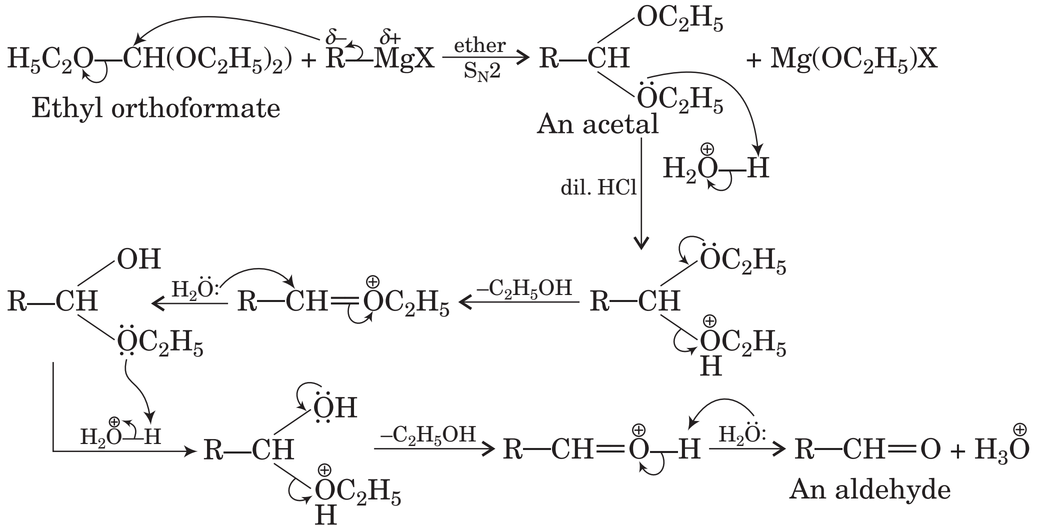
$$\underset{\text{Ethylene chlorohydrin}}{RMgBr + ClCH_2CH_2OH} \longrightarrow RH + ClCH_2CH_2OMgBr \xrightarrow{RMgBr} RCH_2CH_2OMgBr \xrightarrow{H_3O^{\oplus}} RCH_2CH_2OH$$

Two molecules of Grignard reagent are not required if ethylene oxide is used instead of ethylene chlorohydrin.



Ethylene oxide

An aldehyde can be prepared by the reaction between a Grignard reagent and ethyl orthoformate.



In this process, a better yield of aldehyde is obtained since the formation of secondary alcohol is prevented by the formation of acetal.

Ketones may similarly be prepared by using any orthoester, i.e., orthoformic ester.

$$\underset{\text{An orthoester}}{RC(OC_2H_5)_3} + RMgX \xrightarrow{\text{ether}} Mg(OC_2H_5)X + R_2C(OC_2H_5)_2$$

$$\xrightarrow{H_3O^{\oplus}} 2\ C_2H_5OH + \underset{\text{A ketone}}{R_2C{=}O}$$

Primary amines may be prepared by the reaction between *O*-methylhydroxylamine (1 mol) and Grignard reagent (2 mols). The Grignard reagent should be alkylmagnesium chloride or bromide, but not iodide.

$$2\ RMgCl + \underset{\substack{O\text{-Methylhydroxyl}\\ \text{amine}}}{CH_3ONH_2} \xrightarrow{\text{ether}} RNHMgCl + RH + Mg(OCH_3)Cl$$

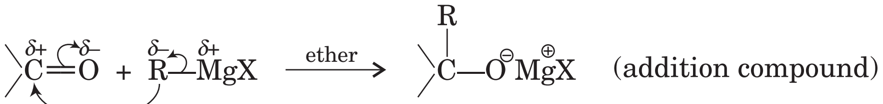
$$RNHMgCl \xrightarrow{H_3O^{\oplus}} \underset{\text{A primary amine}}{R\,NH_2 + MgCl_2}$$

A primary amine containing a tertiary alkyl group may be prepared by using chloramine.

$$\underset{\text{Chloramine}}{ClNH_2} + R{-}MgX \xrightarrow{\text{ether}} \underset{\text{A primary amine}}{R{-}NH_2} + MgXCl$$

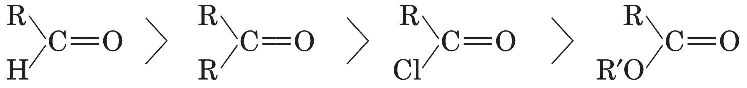
For example: $$ClNH_2 + Me_3C{-}MgCl \xrightarrow{\text{ether}} \underset{\textit{tert}\text{-Butylamine}}{Me_3C{-}NH_2} + MgCl_2$$

(b) Nucleophilic addition reactions Grignard reagents, being nucleophilic in character, add to the carbonyl group of aldehydes ketones, esters, anhydrides and amides. In these reactions, the alkyl group becomes bonded to the carbonyl carbon as a carbanion and the magnesium halide to the oxygen atom of the carbonyl group. The reaction results in formation of an addition compound (a halomagnesium alkoxide).



A halomagenesium alkoxide

In fact, the reactivity of different functional groups towards Grignard reagent is different. The order of reactivity of various compounds containing >C=O group follows the sequence:

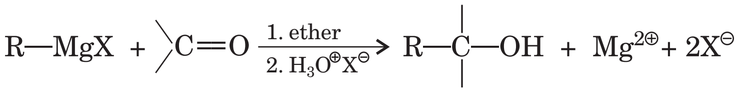


Aldehyde Ketone Acyl chloride Ester

All the above-mentioned >C=O groups are more reactive than the halogen of alkyl halides (—CH_2X), but are less reactive than the active hydrogen. For example, when 4-hydroxy-2-butanone is allowed to react with 1 mol of Grignard reagent, it is the active hydrogen that reacts but the >C=O group remains unaffected.

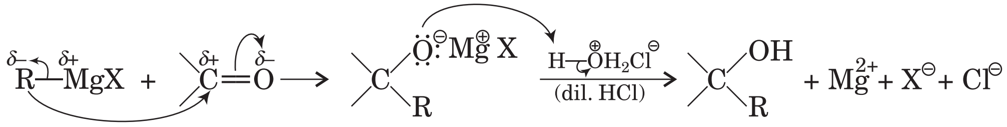
$$\underset{\text{4-Hydroxy-2-butanone}}{CH_3COCH_2CH_2OH} + \underset{\text{(1 mol)}}{CH_3MgI} \longrightarrow CH_3COCH_2CH_2OMgI + \underset{\text{Methane}}{CH_4\uparrow}$$

(i) Reaction with carbonyl compounds and synthesis of alcohols Grignard reagents react with carbonyl compounds (aldehydes and ketones) to form alcohols in the following way:



$$R—MgX + \rangle C=O \xrightarrow[\text{2. } H_3O^{\oplus}X^{\ominus}]{\text{1. ether}} R—\overset{|}{\underset{|}{C}}—OH + Mg^{2\oplus} + 2X^{\ominus}$$

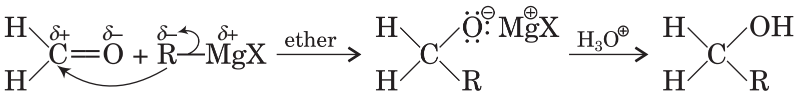
Mechanism:



Grignard reagent Carbonyl compound Halomagnesium alkoxide Alcohol

From the above general scheme, it becomes evident that the class of alcohol obtained from a Grignard reagent and a carbonyl compound depends on the number of hydrogen atoms attached to the carbonyl carbon atoms, i.e., upon the type of the carbonyl compound used.

Formaldehyde, HCHO (the carbonyl carbon bears two hydrogen) yields primary alcohols; other aldehydes, RCHO (the carbonyl carbon bears one hydrogen and one alkyl group) yield secondary alcohols; and ketones, R_2CO (the carbonyl carbon bears no hydrogen) yield tertiary alcohols.



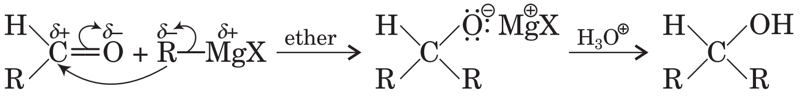
Formaldehyde

A 1° alcohol

For example: $HCHO + CH_3MgI \xrightarrow{\text{ether}} CH_3CH_2OMgI \xrightarrow{H_3O^{\oplus}} CH_3CH_2OH$

Methylmagnesium iodide

Ethyl alcohol



An aldehyde

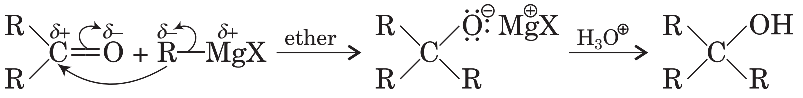
A 2° alcohol

For example: $CH_3CHO + CH_3MgI \xrightarrow{\text{ether}} (CH_3)_2CHOMgI \xrightarrow{H_3O^{\oplus}} (CH_3)_2CHOH$

Acetaldehyde

2-Propanol

If the alkyl groups of the secondary alcohol are different, it can be prepared by using RCHO + R′MgX) or (R′CHO + RMgX), i.e., by using two sets of reagents.



A 3° alcohol

For example: $CH_3COCH_3 + CH_3MgI \xrightarrow{\text{ether}} (CH_3)_3COMgI \xrightarrow{\text{aq. } NH_4Cl} (CH_3)_3COH$

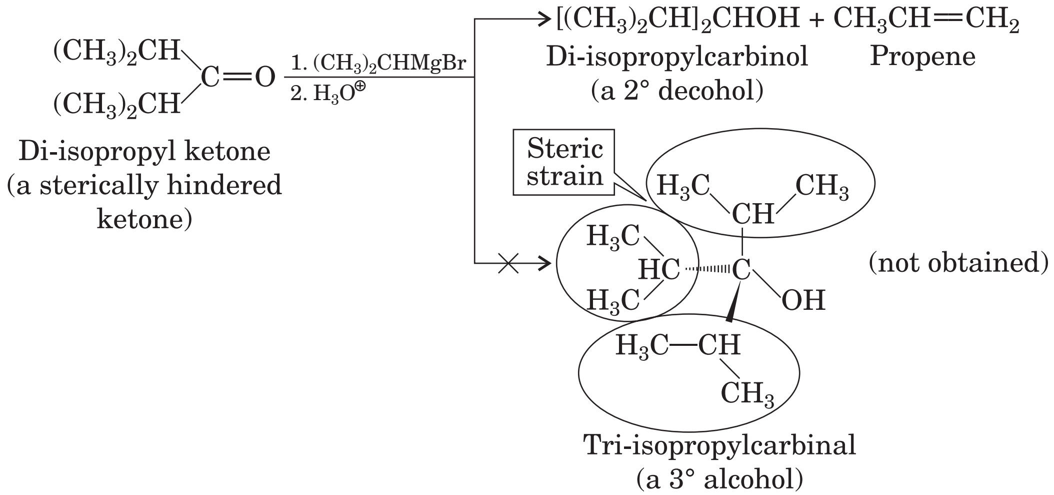
Acetone

tert-Butyl alcohol

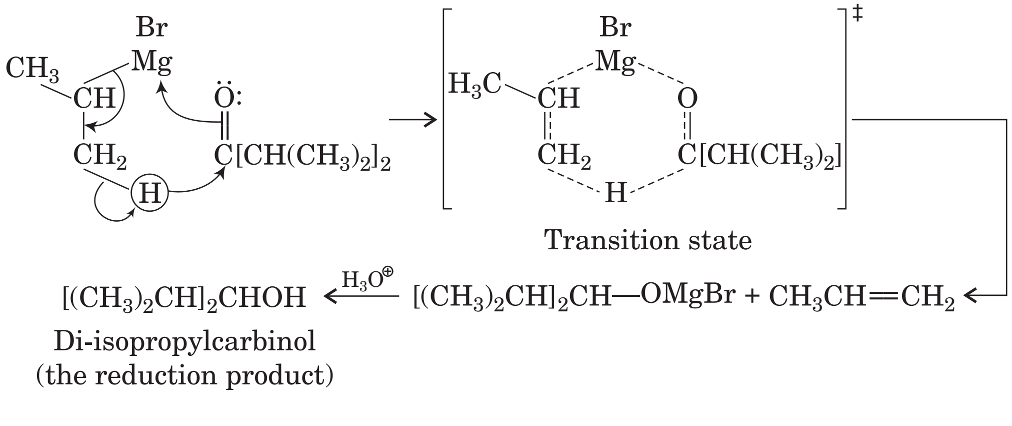
Since the resulting alcohol is tertiary, it is very much susceptible to acid-catalysed dehydration. So, in that case, an aqueous solution NH_4Cl is often used and this is because this solution is acidic enough to convert ROMgX to ROH while not allowing acid-catalysed reactions of the resulting 3° alcohol.

If there are two types of alkyl group in the 3° alcohol, it can be prepared by using two sets of reagents: (R_2CO + R′MgX) or (RCOR′ + RMgX). However, if all the three alkyl groups of the desired tertiary alcohol are different, it can be prepared by using three sets of reagents: (R′COR″ + RMgX), (RCOR″ + R′MgX) or (RCOR′ + R″MgX). However, which combination is more appropriate depends on the availability and cost of the reagents.

Grignard reagent as reducing agent (abnormal Grignard reaction) When the R group of the Grignard reagent and the groups attached to the carbonyl carbon of a ketone are highly branched, normal addition reaction does not take place due to steric interaction involved during nucleophilic attack. In that case, reduction takes place if the Grignard reagent contains a hydrogen on the carbon adjacent to the point of attachment of —MgX (i.e., a β-hydrogen). For example, when isopropylmagnesium bromide is allowed to react with di-isopropyl ketone, no tri-isopropylcarbinol (a tertiary alcohol) is obtained; instead, di-isopropylcarbinol (a secondary alcohol) is obtained through reduction.



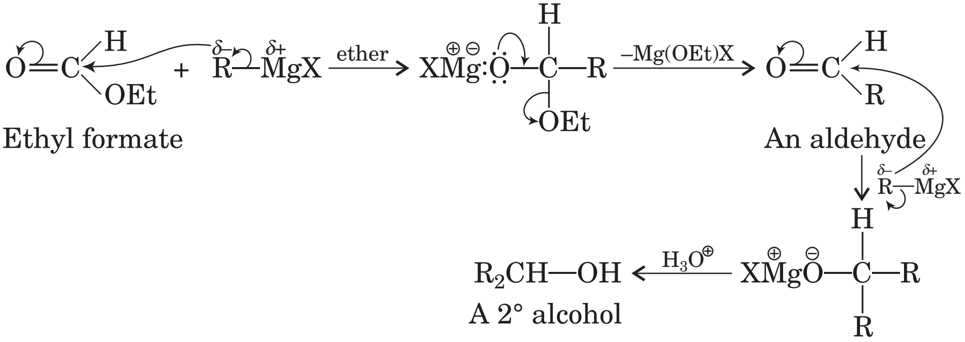
This abnormal reaction may be explained by the transfer of a hydride ion ($H^{\ominus}$) from the Grignard reagent via a six-centred transition state.



It is to be noted that Grignard reagents without a β-H, such as CH_3MgX or C_6H_5MgX, cannot act as reducing agents.

(ii) Reaction with carboxylic acid derivatives Carboxylic acid derivatives like RCOCl, RCOOR or $RCONR_2$ have reasonably good leaving group ($Cl^{\ominus}$, $RO^{\ominus}$, $R_2N^{\ominus}$). So, the primary tetrahedral adduct obtained by the reaction of RMgX with these functional groups stabilizes itself by expelling these leaving groups to give the final product.

- **Reaction with esters and synthesis of secondary and tertiary alcohols** The molar equivalent of a Grignard reagent reacts with formate ester to give a secondary alcohol. The reaction takes place by an addition–elimination mechanism. In the subsequent step, the aldehyde reacts with the second molecule of the Grignard reagent in the usual way to yield a secondary alcohol.

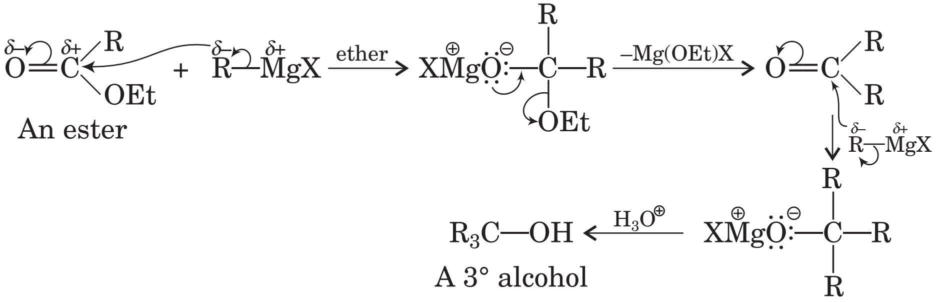


$$\text{e.g., } \text{HCO}_2\text{Et} + 2\text{CH}_3\text{MgI} \xrightarrow{\text{ether}} (\text{CH}_3)_2\text{CHOMgI} \xrightarrow{\text{H}_3\text{O}^{\oplus}} (\text{CH}_3)_2\text{CHOH}$$

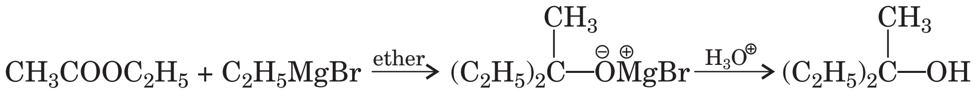
Methylmagnesium iodide 2-Propanol

[An aldehyde can be prepared by allowing a Grignard reagent (1 mol) with ethyl formate (1 mol).]

If in the above reaction any ester other than formate ester is used, a tertiary alcohol containing at least two identical groups is obtained.



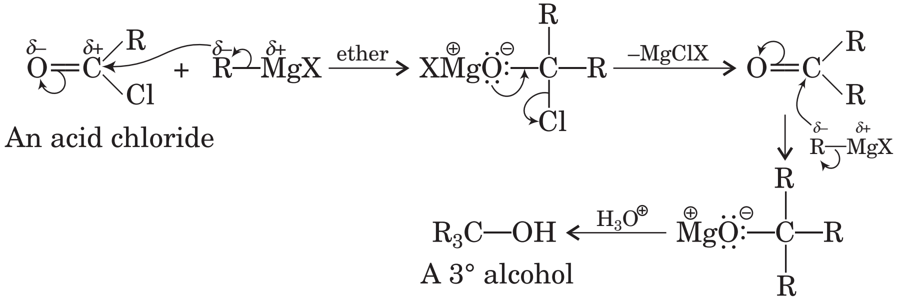
For example:



$$\text{CH}_3\text{COOC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{MgBr} \xrightarrow{\text{ether}} (\text{C}_2\text{H}_5)_2\overset{\text{CH}_3}{\overset{|}{\text{C}}}—\overset{\ominus}{\text{O}}\overset{\oplus}{\text{Mg}}\text{Br} \xrightarrow{\text{H}_3\text{O}^{\oplus}} (\text{C}_2\text{H}_5)_2\overset{\text{CH}_3}{\overset{|}{\text{C}}}—\text{OH}$$

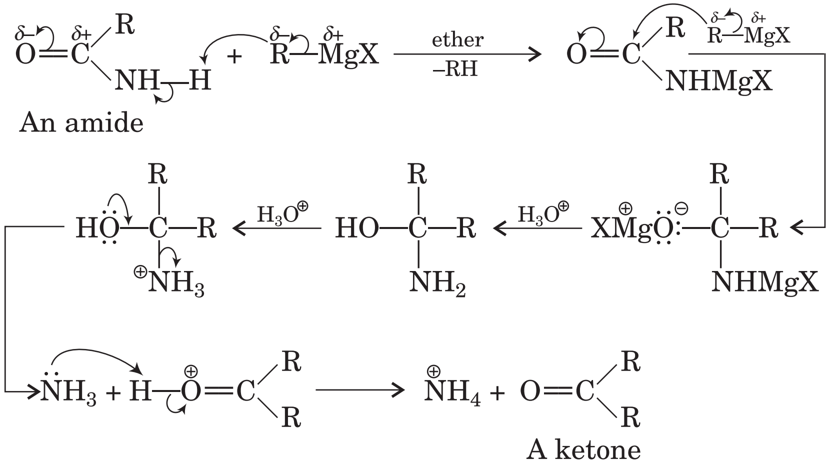
Ethyl acetate 3-Methylpentane-3-ol

- **Reaction with acid chlorides and synthesis of tertiary alcohols** Grignard reagents react with acid chlorides, again in two stages, to yield tertiary alcohols.

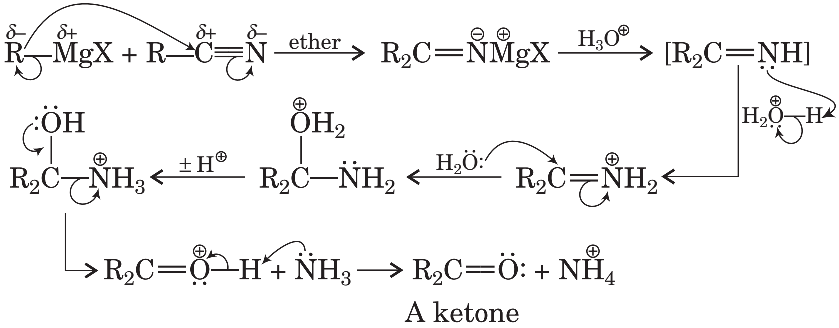


[The intermediate ketone can be isolated if 1 mol of Grignard reagent is used.]

- **Reaction with amides and synthesis of ketones** Two molar equivalents of a Grignard reagent react with one molar equivalent of an amide to form a ketone.

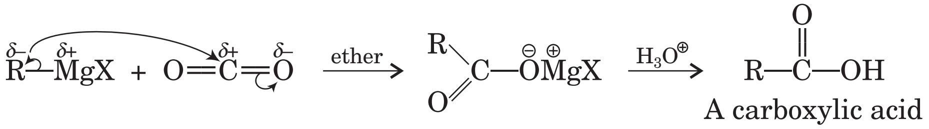


- **Reaction with nitriles and synthesis of ketones** Like the C═O group, the C≡N group is also polarized and the carbon of this group becomes an electrophilic centre. Because of this, a Grignard reagent adds to an alkyl nitrile (RCN) to form a ketimine salt which upon hydrolysis gives the corresponding ketone.

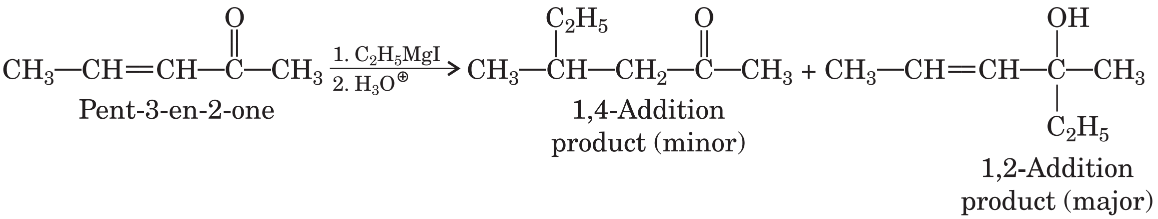


In this preparation, the use of CH_3CN is usually avoided because its α-hydrogen is sufficiently acidic to produce hydrocarbon in reaction with RMgX.

(iii) Reaction with carbon dioxide and synthesis of carboxylic acids When a Grignard reagent is allowed to react with solid carbon dioxide (dry ice) and the resulting complex is decomposed by dilute acid, a carboxylic acid is obtained.



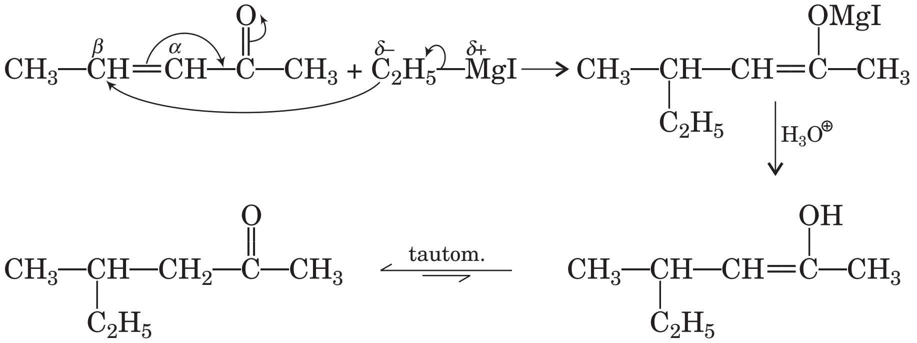
- **Reaction with α,β-unsaturated carbonyl compounds** Grignard reagents add to α, β-unsaturated carbonyl compounds to give a mixture of products due to carbonyl addition (1,2-addition) and conjugate addition (1,4-addition). For example, the reaction of EtMgI with pent-3-en-2-one gives a mixture containing 3 parts of 4-methyl-2-hexanone (1,4-addition product) and 1 part of 2-ethylpent-3-en-2-ol (1,2-addition product).


CH₃—CH═CH—C(=O)—CH₃
Pent-3-en-2-one
1. C₂H₅MgI
2. H₃O⊕
CH₃—CH(C₂H₅)—CH₂—C(=O)—CH₃
1,4-Addition product (minor)
+
CH₃—CH═CH—C(OH)(C₂H₅)—CH₃
1,2-Addition product (major)

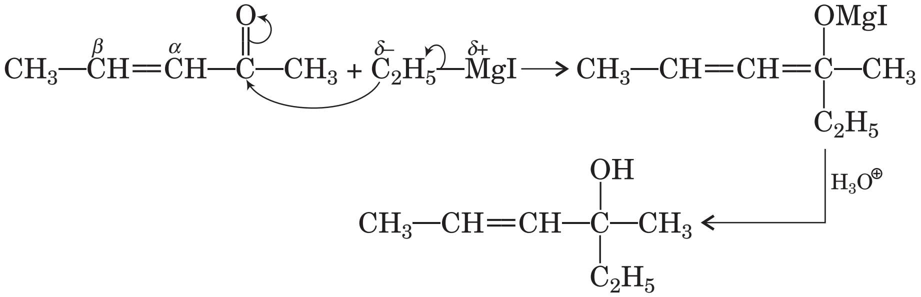
The 1,2-addition is similar to the reaction of a Grignard reagent with a carbonyl compound. The product is an unsaturated alcohol. In 1,4-addition, $R^{\ominus}$ from RMgX attacks at C-4. This is followed by protonation and tautomerisation to yield a carbonyl compound. The overall reaction is an addition to a carbon—carbon double bond.

Mechanism of the reaction:

1,4-Addition:

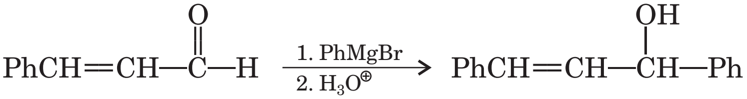

β
α
CH₃—CH═CH—C(=O)—CH₃ + C₂H₅—MgI
δ−
δ+
CH₃—CH(C₂H₅)—CH═C(OMgI)—CH₃
H₃O⊕
CH₃—CH(C₂H₅)—CH═C(OH)—CH₃
tautom.
CH₃—CH(C₂H₅)—CH₂—C(=O)—CH₃

1,2-Addition:



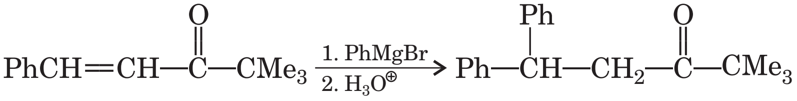
$$CH_3-\overset{\beta}{C}H=\overset{\alpha}{C}H-\overset{O}{\overset{\|}{C}}-CH_3 + \overset{\delta-}{C_2H_5}-\overset{\delta+}{Mg}I \longrightarrow CH_3-CH=CH=\underset{C_2H_5}{\overset{OMgI}{C}}-CH_3 \xrightarrow{H_3O^{\oplus}} CH_3-CH=CH-\underset{C_2H_5}{\overset{OH}{C}}-CH_3$$

The predominant factor in deciding the course of addition is steric hindrance. Therefore, carbonyl addition takes place predominantly in α,β-unsaturated aldehydes while ketones yield conjugate addition as the major product due to steric hindrance. Thus, $PhCH{=}CHCHO$ was found to undergo ≈100% $C{=}O$ addition with PhMgBr, whereas $PhCH{=}CHCOCHC_3$ was found to undergo ≈100% $C{=}C$ addition with the same reagent. This also reflects the decreasing the reactivity of the $C{=}O$ group in the sequence aldehyde > ketone > ester, with consequent increase in the proportion of $C{=}C$ addition.



$$PhCH=CH-\overset{O}{\overset{\|}{C}}-H \xrightarrow[2.\ H_3O^{\oplus}]{1.\ PhMgBr} PhCH=CH-\overset{OH}{\overset{|}{C}}H-Ph$$

1, 2-Addition product
(100%)



$$PhCH=CH-\overset{O}{\overset{\|}{C}}-CMe_3 \xrightarrow[2.\ H_3O^{\oplus}]{1.\ PhMgBr} Ph-\overset{Ph}{\overset{|}{C}}H-CH_2-\overset{O}{\overset{\|}{C}}-CMe_3$$

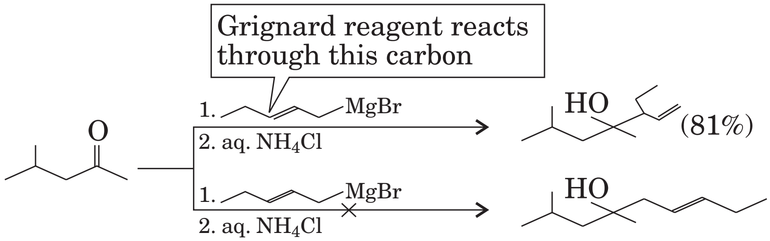
1, 4-Addition product
(100%)

In the presence of a small proportion (<10 mol%) of a copper (I) salt (e.g., cuprous chloride, cuprous acetate) the addition is almost exclusively at the β-carbon, i.e., 1,4-addition. Magnesium organocuprates are the presumed intermediates in such reactions. For example:

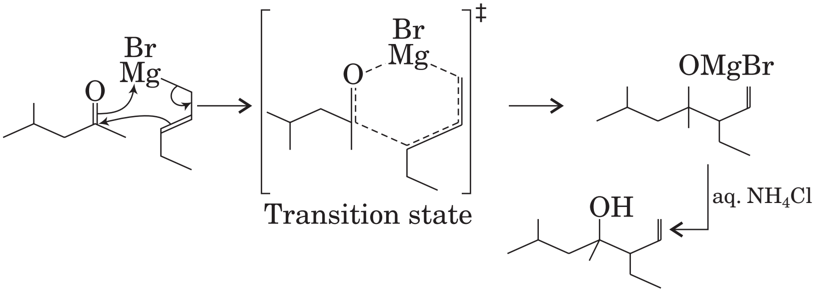
$$PhCH_2MgCl + CH_2{=}CHCO_2Et \xrightarrow[-25°C]{CuCl} Ph(CH_2)_3CO_2C_2H_5$$

(69 %)

Reactions of allylic Grignard reagents with carbonyl compounds An allylic Grignard reagent reacts with a carbonyl compound by a six-membered cyclic transition state. Allylic Grignard reagents actually react as nucleophiles at the end of the allyl system. For example:



Mechanism of the reaction:



2.2.3 Limitations in the use of Grignard Synthesis

Even though the Grignard synthesis is one of the most versatile of all general synthetic procedures, it is not without its limitations. The limitations actually arise from its extraordinary reactivity as a nucleophile and a base. These are as follows:

1. It is not possible to prepare a Grignard reagent from a compound that contains an acidic hydrogen (any hydrogen more acidic than the hydrogen atom of an alkane or alkene). Thus, we cannot, e.g., prepare of Grignard reagent from a compound containing –OH, –NH$_2$, –SH, –COOH or –C≡CH group and this is because the resulting Grignard reagent would immediately be neutralized by the acidic group.
2. Since Grignard reagents are powerful nucleophiles, we cannot prepare a Grignard reagent from any organic halide that contains a $>$C=O, –COOR, –COX, –CONH$_2$ or –CN group. An epoxy group opens up by a Grignard reagent and an NO$_2$ group is reduced by a Grignard reagent. Hence, these two groups also must not be present in the halide molecule.
3. A Grignard reagent reacts rapidly with O$_2$, CO$_2$ and water. So, the reaction system must be protected from O$_2$, CO$_2$ and moisture of air. The alkyl halide, the carbonyl compound and the ether used as solvent must be completely dry and alcohol free. Also, the apparatus must be dry.

2.3 ORGANOLITHIUM COMPOUNDS

2.3.1 Preparation of Organolithium Compounds

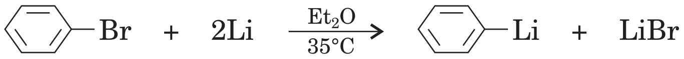
Organolithium compounds are prepared by the reaction (reduction) of organic halides with lithium metal. These reactions are usually carried out in ether solvents, and since organolithium reagents are strong bases and react rapidly with even weak proton sources to form hydrocarbons, care must be taken to exclude moisture. The commonly used ethers are diethyl ether (Et_2O) and tetrahydrofuran ( ).

$$\underset{\text{Alkyl halide}}{R{-}X + 2Li} \xrightarrow{Et_2O} \underset{\text{Alkyllithium}}{R{-}Li} + LiX$$

For example, *tert*-butyl chloride reacts with lithium metal in diethyl ether to give a solution of *tert*-butyllithium.

$$\underset{\textit{tert}\text{-Butyl chloride}}{(CH_3)_3C{-}Cl} + 2Li \xrightarrow[-30°C]{Et_2O} \underset{\substack{\textit{tert}\text{-Butyllithium}\\(75\%)}}{(CH_3)_3C{-}Li} + hiCl$$

The alkyl halide can be primary, secondary, or tertiary. The order of reactivity of halides is RI > RBr > RCl. Fluorides are relatively unreactive and are not generally used in the preparation of alkyllithium. Unlike substitution and elimination reactions, formation of organolithium compounds does not require the halogen bonded to C_{sp3}. Compounds like vinyl and aryl halides, in which the halogen atom is bonded to a C_{sp2}, react in the same way as an alkyl halide. However, the rate is somewhat slower. For example,

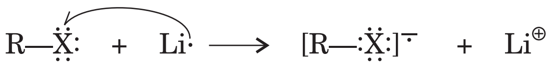


Bromobenzene

Phenyllithium (97%)

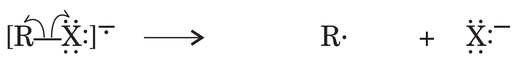
Mechanism of the reaction leading to the formation of R—Li The reaction of an alkyl halide with a metal actually takes place at the metal surface. The mechanism involves the steps as follows:

Step 1: An electron in transferred from lithium to the alkyl halide to form a radical anion.



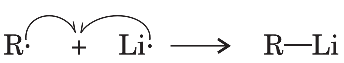
$$\underset{\text{Alkylhalide}}{R{-}\ddot{\underset{..}{X}}:} + Li\cdot \longrightarrow \underset{\text{Radical anion}}{[R{-}:\ddot{\underset{..}{X}}:]^{\dot{-}}} + Li^{\oplus}$$

Step 2: The extra electron in the radical anion occupies an antibonding orbital. This radical anion dissociates to form an alkyl radical and a halide anion.



$$\underset{\text{Radical anion}}{[R{-}\ddot{\underset{..}{X}}:]^{\dot{-}}} \longrightarrow \underset{\text{Alkyl radical}}{R\cdot} + \ddot{\underset{..}{X}}:^{-}$$

Step 3: The alkyl radical readily combines with a lithium atom to form the organolithium compound.

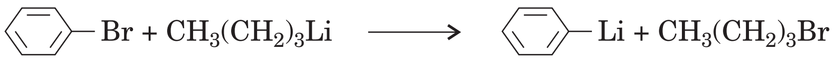


$$\underset{\text{Alkyl radical}}{R\cdot} + Li\cdot \longrightarrow \underset{\text{Alkyllithium}}{R{-}Li}$$

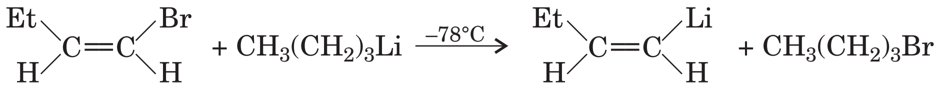
A second method for preparation of organolithium compounds involves a halogen—metal exchange reaction.

$$R-Li + R'-X \rightleftharpoons R-X + R'-Li \ (X = Br, I)$$

For example,



Bromobenzene Phenyllithium



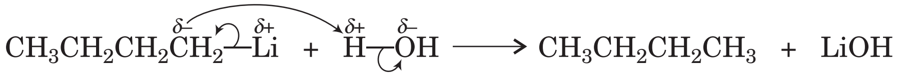
1-Bromo-but-l-ene 1-Butenyllithium

The exchange usually occurs with retention of configuration of the parent compounds.

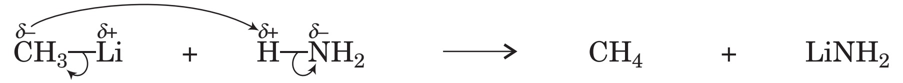
2.3.2 Reactions of Organolithium Compounds

2.3.2.1 Reaction as a Base

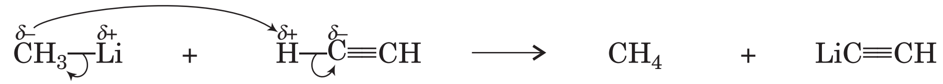
Organolithium compounds are very strong bases. They readily abstract a proton from any compound that has an acidic hydrogen atom attached to an electronegative atom like oxygen, nitrogen, sulphur and even C_{sp}. In fact, organometallic compounds acting as carbanions (carbanions rank among the strongest bases) will abstract proton from any substance more acidic than an alkane. For example,



Butyllithium (Stronger base) Water (Stronger acid $pK_a = 15.7$) Butane (Weaker acid $pK_a \approx 62$) Lithium hydroxide (Weaker base)

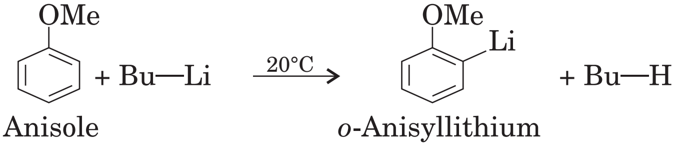


Methyllithium (Stronger base) Ammonia (Stronger acid $pK_a = 36$) Methane (Weaker acid $pK_a = 60$) Lithium amide (Weaker base)

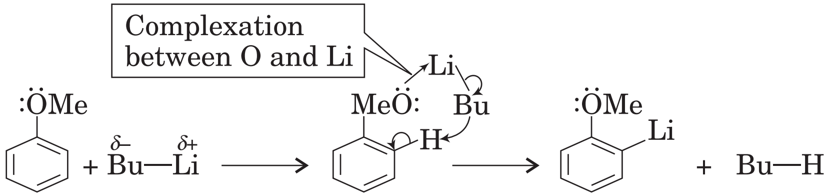


Methyllithium (Stronger base) Acetylene (Stronger acid $pK_a = 26$) Methane (Weaker acid $pK_a = 60$) Ethynyllithium (Weaker base)

Ortholithiation (formation of Ar—Li by deprotonating *ortho* C—H bonds in aromatic rings) Butyllithium deprotonates an sp^2-hybridized carbon atom to give an aryllithium. It works because the protons attached to sp^2 carbons are more acidic than protons attached to sp^3 carbons. For example,

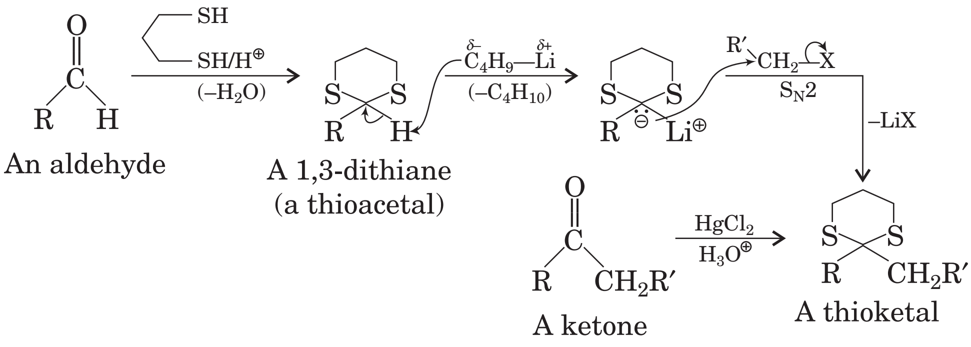


However, there is another factor involved as well. Such a reaction requires a functional group containing oxygen (or nitrogen) next to the proton to be removed. This functional group directs butyllithium to attack the adjacent proton. It does this by forming a complex with the Lewis acidic lithium atom. Since it is only the protons *ortho* to the functional group that can be removed, the reaction is known as *ortholithiation*. The reaction occurs as follows:

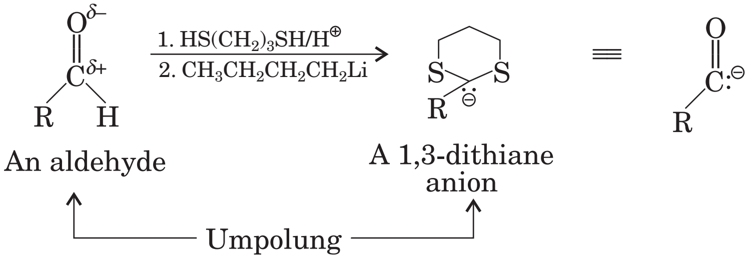


This is what is called directed *orthometalation*. The reaction is useful because the starting material does not need to contain a halogen atom.

Use of RLi as a base and concept of Umpolung: Preparation of 1,3-dithianes (thioacetals) by treating an aldehyde with 1,3-propanedithiol in the presence of a trace acid, alkylation of the dithiane through the formation of its anion by strong bases such as butyllithium and hydrolysis of the product (a thioketal) to give a ketone provides a method for converting an aldehyde to ketone.



In these syntheses involving 1,3-dithiane, the usual mode of reaction of an aldehyde is reversed. Normally, the carbonyl carbon atom is partially positive, i.e., it is electrophilic and it reacts with nucleophiles. When the aldehyde is converted to a 1,3-dithiane and treated with butyllithium, the same carbon atom becomes negatively charged and reacts with electrophiles. This reversal of polarity of the carbonyl carbon atom is called *umpolung* (German for "polarity reversal"). The 1,3-dithiane anion is, therefore, a synthetic equivalent of an anionic carbonyl carbon atom (an aldehyde carbanion).

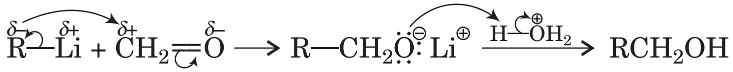


2.3.2.2 *Reaction as a Nucleophile*

Organolithium compounds are more strongly nucleophilic than the corresponding Grignard reagents. They undergo all the addition reactions of the latter, in some cases more efficiently.

(a) Reaction with carbonyl compounds and synthesis of alcohols Reactions of alkyl or aryllithiums with carbonyl compounds are similar to those of Grignard reagents, i.e., with formaldehyde they give primary alcohols, with other aldehydes they yield secondary alcohols and with ketones they produce tertiary alcohols.

(i)



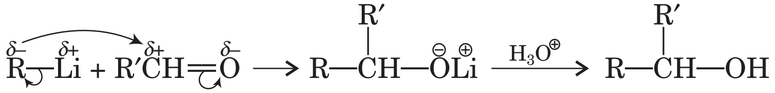
$$\overset{\delta-}{R}-\overset{\delta+}{Li} + \overset{\delta+}{C}H_2=\overset{\delta-}{O} \longrightarrow R-CH_2\ddot{\underset{..}{O}}{}^{\ominus}\ Li^{\oplus} \xrightarrow{H-\overset{\oplus}{O}H_2} RCH_2OH$$

Formaldehyde A primary alcohol

For example: $CH_3-Li + CH_2=O \longrightarrow CH_3CH_2OLi \xrightarrow{H_3O^{\oplus}} CH_3CH_2OH$

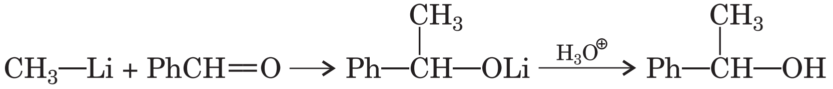
Ethyl alcohol

(ii)



$$\overset{\delta-}{R}-\overset{\delta+}{Li} + R'\overset{\delta+}{C}H=\overset{\delta-}{O} \longrightarrow R-\overset{R'}{\overset{|}{C}H}-\overset{\ominus}{O}\overset{\oplus}{Li} \xrightarrow{H_3O^{\oplus}} R-\overset{R'}{\overset{|}{C}H}-OH$$

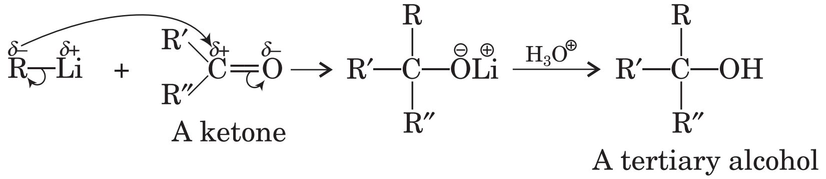
An aldehyde A secondary alcohol



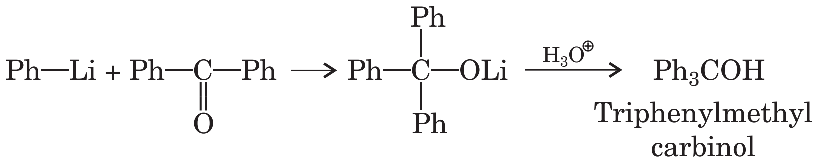
For example: $CH_3-Li + PhCH=O \longrightarrow Ph-\overset{CH_3}{\overset{|}{C}H}-OLi \xrightarrow{H_3O^{\oplus}} Ph-\overset{CH_3}{\overset{|}{C}H}-OH$

1-Phenylethanol

(iii)



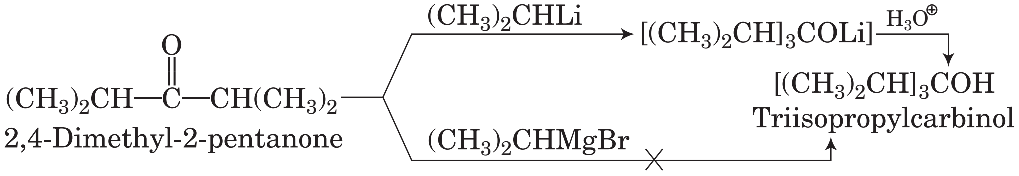
For example:



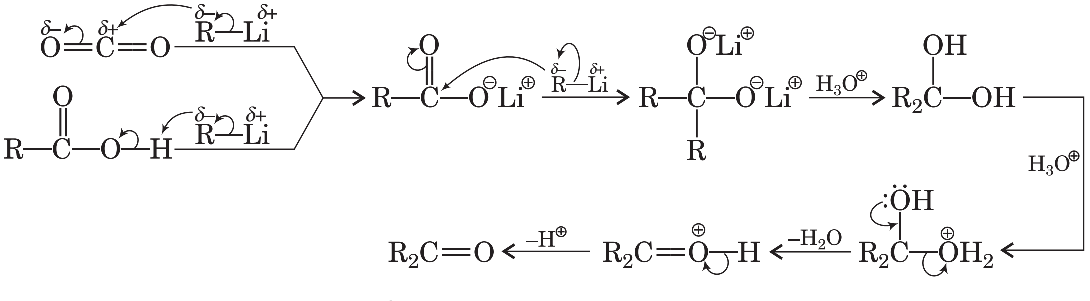
$$\mathrm{Ph{-}Li + Ph{-}\underset{\underset{O}{\|}}{C}{-}Ph \longrightarrow Ph{-}\overset{\overset{Ph}{|}}{\underset{\underset{Ph}{|}}{C}}{-}OLi \xrightarrow{H_3O^{\oplus}} Ph_3COH}$$

Triphenylmethyl carbinol

Alkyllithiums have an advantage over Grignard reagents. While the latter fail to give tertiary alcohols when treated with sterically hindered ketones, the former react with such ketones giving the corresponding tertiary alcohols. For example,



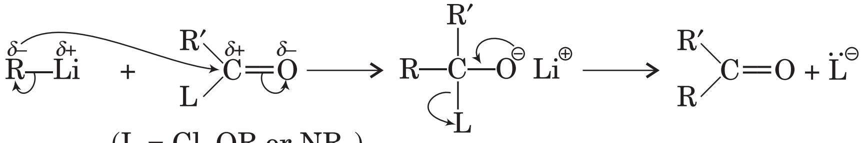
(b) Reaction with carbon dioxide (carbonation) When an alkyllithium is treated with CO_2, the alkyl group adds to the carbonyl group of CO_2 to form a carboxylate anion. Even though the carboxylate anion is resonance stabilized, it undergoes nucleophilic attack by a second molecule of RLi, to yield a ketone. This is not observed in the case of relatively less reactive RMgX. A carboxylic acid (RCOOH) also reacts with two molecules of R—Li to give a ketone.



$$\text{e.g., } \mathrm{Ph{-}Li + PhCOOH \xrightarrow[5\text{–}6\ h]{ether} PhCOPh}$$

Benzophenone
(70%)

(c) Reaction with carboxylic acid derivatives Carboxylic acid derivatives like RCOCl, RCOOR or $RCONR_2$ have reasonably good leaving groups ($Cl^{\ominus}$, $\overset{\ominus}{O}R$ or $\overset{\ominus}{N}R_2$). So, the primary tetrahedral adduct obtained by the reaction of R—Li with these functional groups stabilizes itself by expelling these leaving groups to give the final product.

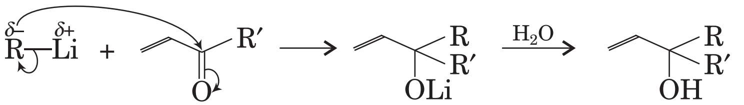


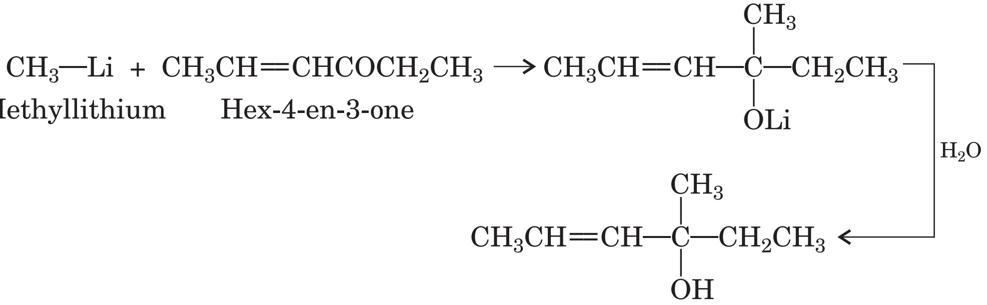
(L = Cl, OR or NR_2)

For example: $CH_3(CH_2)_9Li + CH_3CONMe_2 \longrightarrow CH_3(CH_2)_9COCH_3$
2-Dodecanone (88%)

$CH_3(CH_2)_9Li + HCONMe_2 \longrightarrow CH_3(CH_2)_9CHO$
Undecanal (60%)

(d) Reaction with *α,β*-unsaturated carbonyl compounds Due to higher ionic nature of R—Li bond, the organolithium compounds act as harder nucleophile compared to RMgX and hence preferentially attack the harder electron-deficient carbonyl carbon atom.





For example: $CH_3—Li + CH_3CH{=}CHCOCH_2CH_3 \longrightarrow CH_3CH{=}CH—\underset{OLi}{\overset{CH_3}{C}}—CH_2CH_3 \xrightarrow{H_2O} CH_3CH{=}CH—\underset{OH}{\overset{CH_3}{C}}—CH_2CH_3$

Methyllithium Hex-4-en-3-one

3-Methylhex-4-en-3-ol

2.4 ORGANOCUPRATES OR GILMAN REAGENTS

New carbon—carbon bond can be formed by using organometallic compounds that has a transition metal as its metal atom. The first organometallic compounds used in coupling reaction (coupling of two alkyl groups leading to a hydrocarbon) were organocuprates or lithium dialkylcuprates (R_2CuLi). These are also called *Gilman reagents* after their discoverer, Henry Gilman. Organocuprates are much less reactive than organolithium compounds or Grignard reagents because the C—Cu bond is relatively less polar than the C—Li or C—Mg bond, i.e., Cu is closer in electronegativity to carbon than is lithium or magnesium. Only one of the two alkyl groups in an organocuprate is used as a nucleophile in its reactions.

2.4.1 Preparation of Lithium Dialkylcuprates (Gilman reagents)

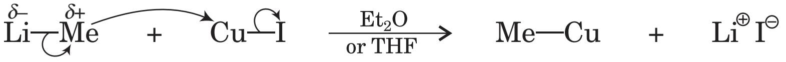
A lithium dialkylcuprate can be prepared by the reaction of two equivalents of an organolithium reagent with cuprous iodide in diethyl ether or THF. Transmetallation occurs because Cu is more electronegative (1.8) than Li (1.0). For example:

$$\underset{\text{Methyllithium}}{2\,CH_3Li} + CuI \xrightarrow[\text{or } Et_2O]{\text{THF}} \underset{\substack{\text{Lithium dimethylcuprate}\\ \text{(a \textit{Gilman reagent})}}}{(CH_3)_2CuLi} + LiI$$

Lithium diarylcuprates are prepared in the same way as R_2CuLi.

Mechanism of the reaction:

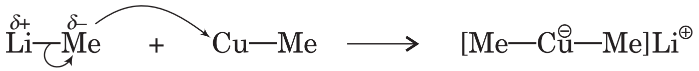
Step 1: One molar equivalent of methyllithium displaces iodide from copper(I) iodide to give methylcopper(I) species. The driving force for this reaction is the preference of lithium, the more electropositive metal, to exist as an ionic compound ($Li^{\oplus}I^{\ominus}$).



$$\overset{\delta-}{Li}—\overset{\delta+}{Me} + Cu—I \xrightarrow[\text{or THF}]{Et_2O} Me—Cu + Li^{\oplus}I^{\ominus}$$

Methyllithium Copper(I) iodide Methylcopper Lithium iodide

Step 2: The second molar equivalent of methyllithium adds to methylcopper to give a negatively charged $Me_2Cu^{\ominus}$ species called dimethylcuprate. It is formed as its lithium salt, lithium dimethylcuprate.



$$\overset{\delta+}{Li}—\overset{\delta-}{Me} + Cu—Me \longrightarrow [Me—\overset{\ominus}{Cu}—Me]Li^{\oplus}$$

Methyllithium Methylcopper Lithium dimethylcuprate

2.4.2 Reactions of Lithium Dialkylcuprates

Because of the low ionicity of C—Cu bond, lithium dialkylcuprates are not readily attacked by weak acids like water and alcohol. These reagents are formally nucleophilic and like other organometallic compounds may be represented by the synthon $R^{\ominus}$. In fact, these reagents can be conceptualized as an alkyl anion complexed to copper: $R—Cu \cdots :\overset{\ominus}{R}\overset{\oplus}{Li}$. They typically react with acid chlorides, aldehydes and alkyl halides (except tertiary alkyl halides). However, they do not react with ketones, esters and nitriles. Some important reactions of cuprates are as follows.

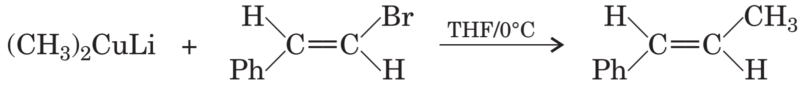
2.4.2.1 Coupling Reactions

Lithium dialkylcuprates react with primary alkyl halides to yield alkanes. This method for the synthesis of hydrocarbons is known as *Corey–Posner, whitesides–House synthesis*. For example:

$$\underset{\text{Lithium dimethylcuprate}}{(CH_3)_2CuLi} + \underset{\text{1-Iododecane}}{CH_3(CH_2)_8CH_2I} \xrightarrow[S_N2]{Et_2O/0°C} \underset{\text{Undecane}}{CH_3(CH_2)_8CH_2CH_3}$$

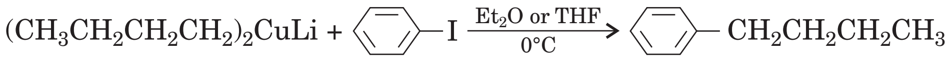
Due to low ionic character of the C—Cu bond, the low oxidation potential of Cu(I)—Cu(II) reaction and ability of Cu to form clusters contribute to the ability of dialkylcuprates to undergo coupling reactions giving C—C bond formation.

The most frequently used organocuprates are those in which the alkyl group is primary. Steric hindrance makes secondary and tertiary dialkylcuprates relatively less reactive. The reaction of organocuprate reagents with alkyl halides follows the usual S_N2 order: $CH_3 > 1° > 2° > 3°$ and I > Br > Cl > F. *p*-Toluenesulfonates are somewhat more reactive than halides. Since the dialkylcuprate reagent and the alkyl halide should both be primary in order to have a good yield of coupled products, the reaction is usually used for the formation of $RCH_2—CH_2R'$ and $RCH_2—CH_3$ bonds in alkanes. There is probably more than one mechanism by which dialkylcuprates react with organic halides and this is because vinyl and aryl halides, which are known to be very unreactive in S_N2 reaction, are found to react smoothly with lithium dialkylcuprates.



Lithium dimethylcuprate — *trans*-1-Bromo-2-phenylethene — *trans*-1-Phenylpropene (81%)

The substitution is stereospecific, i.e., the configuration of the double bond is retained in the product.

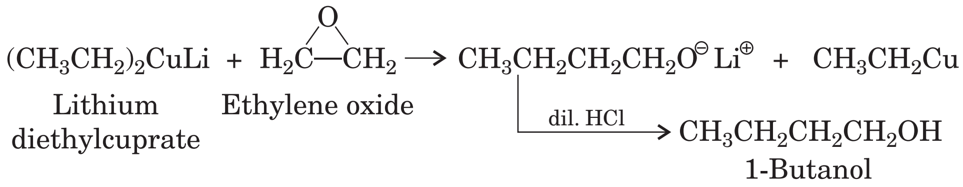


Lithium dibutylcuprate — Iodobenzene — Butylbenzene (75%)

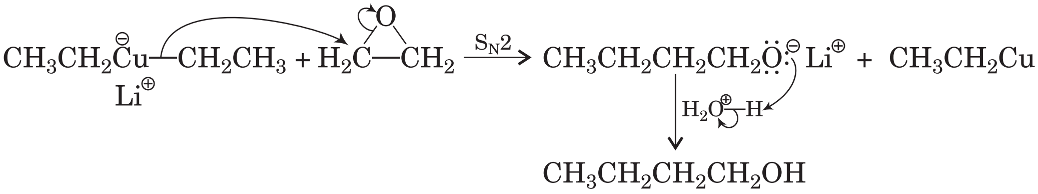
Organocuprates can even replace halogen in compounds that contain other functional groups (e.g., C=O, C≡N, etc.).

2.4.2.2 Reaction with Epoxides

Dialkylcuprates react with epoxides (a substitution reaction) to yield, after acidification, a primary alcohol with two more carbons than in the alkyl group of the reagent. For example:



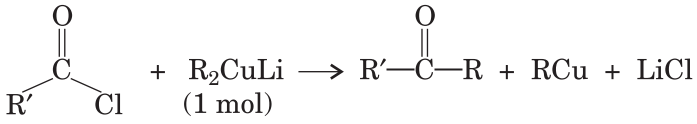
Mechanism:


CH3CH2Cu⊖—CH2CH3 Li⊕ + H2C—CH2 (O)
SN2
CH3CH2CH2CH2O⊖ Li⊕ + CH3CH2Cu
H2O⊕—H
CH3CH2CH2CH2OH

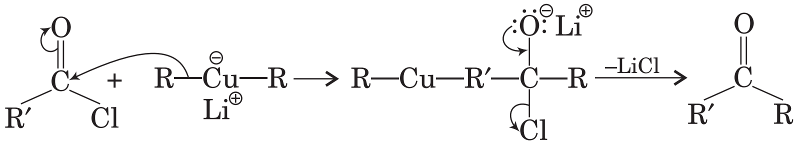
If one carbon of the epoxide contains an alkyl substituent, then attack takes place at the less crowded other carbon.

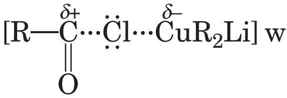
2.4.2.3 Reaction with Acid Chlorides

Lithium dialkylcuprates react with acid chlorides (in which $Cl^{\ominus}$ is a good leaving group) to yield ketones. This method for the synthesis of ketones is especially useful because, unlike RLi or RMgX, dialkylcuprates do not attack ketones. Because ketones are much less reactive than acid chlorides towards dialkylcuprates, they do not react further.



Mechanism:

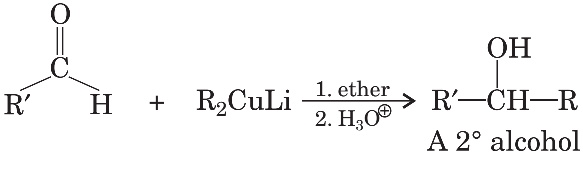




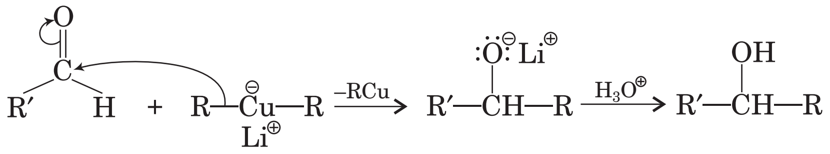
The greater reactivity of an acid chloride is due to formation of a complex like $[R—\underset{\underset{O}{\|}}{\overset{\delta+}{C}}\cdots\ddot{\underset{..}{C}}l\cdots\overset{\delta-}{C}uR_2Li]$ with greater δ^+ on the carbonyl carbon.

2.4.2.4 Reaction with Aldehydes

Though ketones are not easily attacked by dialkylcuprates, the aldehydes are readily attacked to yield alcohols as the final product.

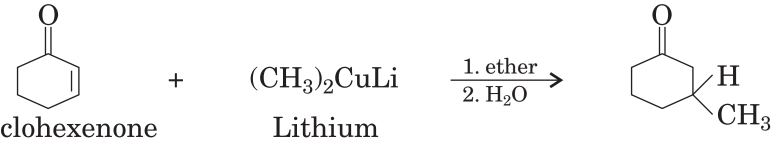


Mechanism:



2.4.2.5 *Reaction with α,β-unsaturated Carbonyl Compounds*

Lithium dialkylcuprates react with α,β-unsaturated carbonyl compounds to give almost invariably, the products of conjugate addition. For example:



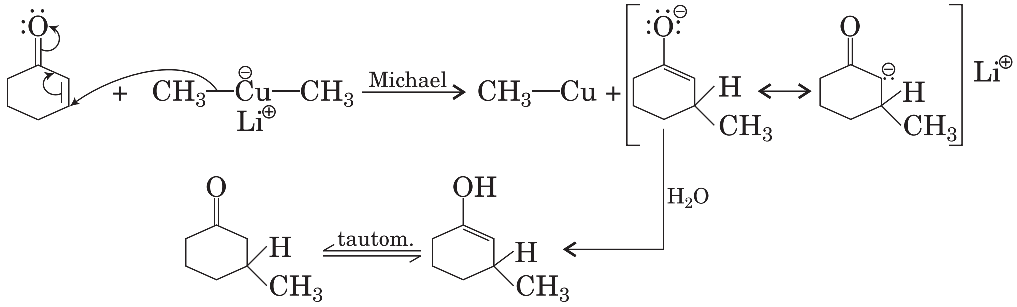
2-Cyclohexenone

Lithium dimethylcuprate

3-Methylcyclohexanone (97%)

Due to higher percentage of covalency in C—Cu bond in dialkylcuprates these compounds act as sources of soft nucleophilic $R^{\ominus}$ ions. These soft nucleophiles preferentially attack the soft β-carbon of an α,β-unsaturated carbonyl compound in a conjugate addition reaction.

Mechanism:



2.5 ORGANOZINC COMPOUNDS

Organozinc compounds are relatively unstable and are not used much in preparative organic chemistry.

2.5.1 Preparation of Organozinc Compounds

2.5.1.1 *From Alkyl Halides*

Treatment of freshly prepared Zn fillings with alkyl iodides results in formation of alkylzinc iodides (RZnI). These upon distillation in CO_2 atmosphere give dialkylzinc compounds.

$$RI + Zn \longrightarrow RZnI \quad ; \quad 2\,RZnI \xrightarrow[\text{distill.}]{CO_2} \underset{\text{Dialkylzinc}}{R_2Zn} + ZnI_2$$

In this reaction, high boiling ethers are used as solvents and Zn—Cu alloy is employed in place of metallic zinc. For example,

$$2\,C_2H_5I + 2\,Zn \longrightarrow 2\,C_2H_5ZnI \xrightarrow[\text{distill.}]{CO_2} \underset{\text{Diethylzinc}}{Zn(C_2H_5)_2} + ZnI_2$$

2.5.1.2 *By Transmetallation Reaction*

Organozinc compounds can also be prepared by transmetallation reaction.

$$2RLi + ZnCl_2 \longrightarrow R_2Zn + 2LiCl$$

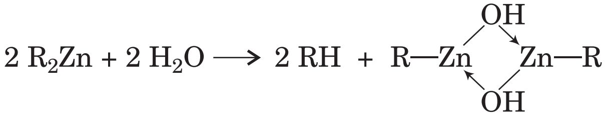
Organozinc compounds are nonpolar low boiling liquids or low melting solids, soluble in organic solvents. The lower zinc compounds are inflammable in air, and so, they are prepared and used under CO_2 atmosphere.

2.5.2 Reactions of Organozinc Compounds

The chemical reaction of organozinc compounds are similar to those of Grignard reagents. However, they are less reactive than Grignard reagents. For instance, they do not react with CO_2 (unlike Grignard reagents) and react only slowly with ketones, esters and cyanides. Some important reactions of organozinc compounds are as follows.

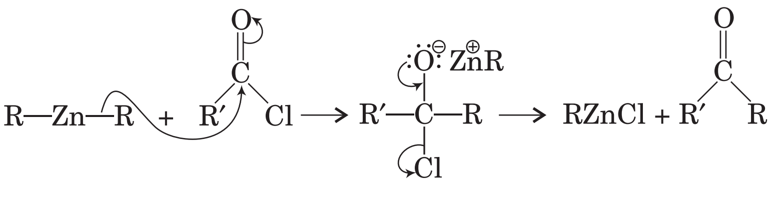
2.5.2.1 *Reaction with Water*

Dialkylzinc compounds react readily with water forming hydrocarbons.



2.5.2.2 *Reaction with Acid Chlorides*

Acid chlorides react with organozinc compounds to give ketones. Since ketones react with organozinc compounds extremely slowly, they can easily be isolated from the reaction mixture.

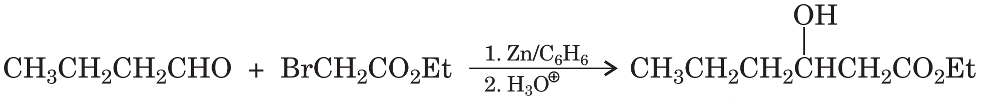


The reactions of dialkylzinc compounds with esters, cyanide, etc. is extremely slow, and hence, they have practically no synthetic importance.

2.5.2.3 Reformatsky Reaction (formation of β-hydroxyesters)

The reaction of an α-halo ester, usually an α-bromo ester, with an aldehyde or ketone in the presence of zinc in an inert solvent (e.g., ether, benzene, toluene, THF, etc.) to produce, after hydrolysis, β-hydroxy esters is called the *Reformatsky reaction*.

Example:



$$\mathrm{CH_3CH_2CH_2CHO + BrCH_2CO_2Et \xrightarrow[2.\ H_3O^{\oplus}]{1.\ Zn/C_6H_6} CH_3CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_2CO_2Et}$$

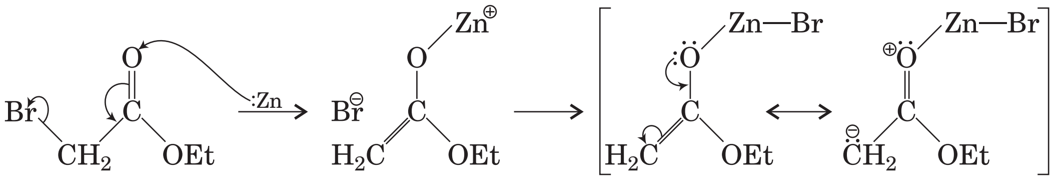
Butanal Ethyl bromoacetate A β-hydroxyester

The carbonyl compound used may be aliphatic, aromatic or heterocyclic and may contain various functional groups.

Since organozinc compounds are much less reactive than RMgX and RLi, they chemoselectively attack the carbonyl group of an aldehyde or a ketone and not the ester group. Therefore, self-condensation reaction does not take place. By taking this advantage of low reactivity of organozinc compounds over organomagnesium or organolithium compounds β-hydroxyesters can be prepared by the Reformatsky reaction.

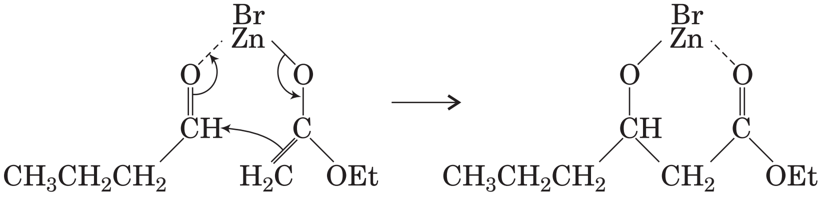
Mechanism of the reaction The mechanism of the reaction involves the steps as follows:

Step 1: The α-bromo ester reacts with zinc in benzene to produce a zinc enolate.

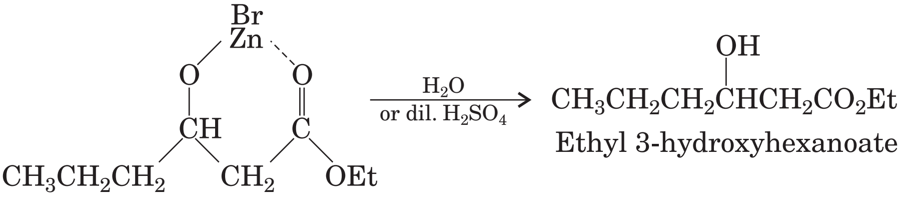


zinc enolate

Step 2: The zinc enolate adds to the carbonyl group of the aldehyde to form a zinc alkoxide.



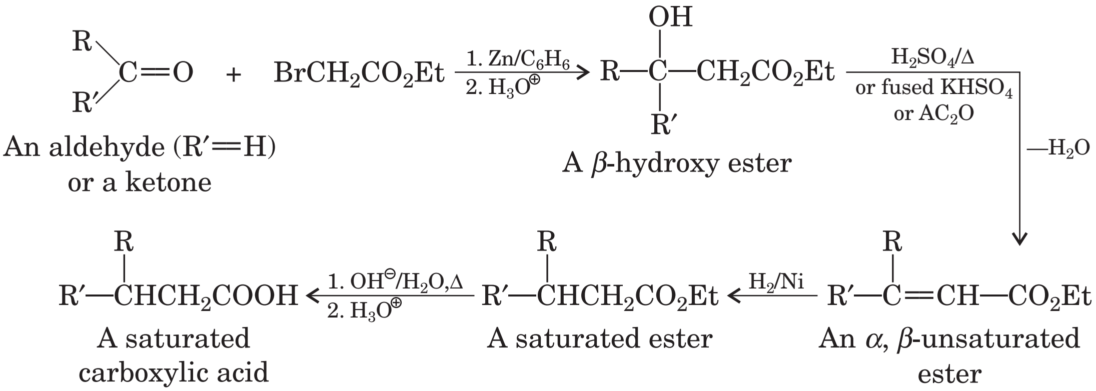
Step 3: The alkoxide on hydrolysis produces a β-hydroxy ester.



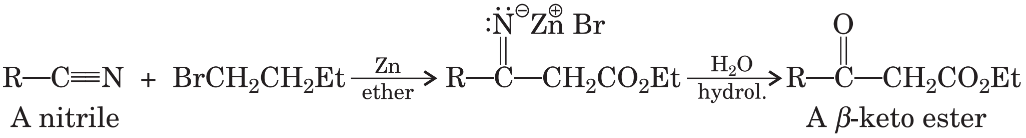
Ethyl 3-hydroxyhexanoate

Synthetic application of the reaction Some important applications of the reaction are as follows:

(i) The hydroxy ester obtained in the Reformatsky reaction can be dehydrated to yield α,β-unsaturated esters. Catalytic hydrogenation of the unsaturated esters followed by hydrolysis yields saturated carboxylic acids. The complete procedure thus constitutes a useful two-carbon chain extension process.

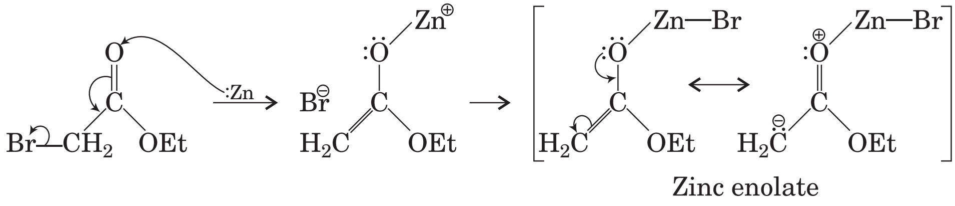


(ii) A modification of the Reformatsky reaction is the *Blaise reaction* in which a nitrile is made to react with an α-halo ester to get a β-keto ester.

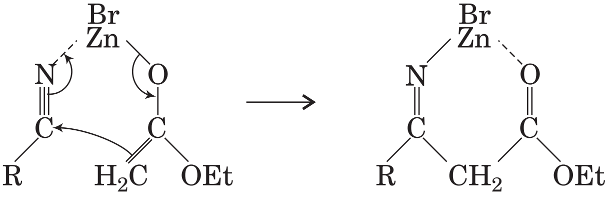


Mechanism:

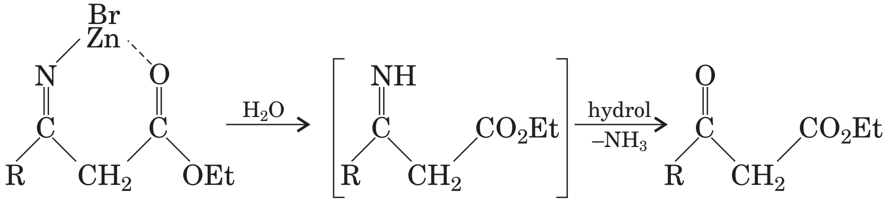
Step 1:



Step 2:

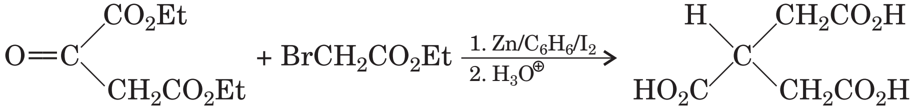


Step 3:



An imine
(susceptible to hydrolysis)

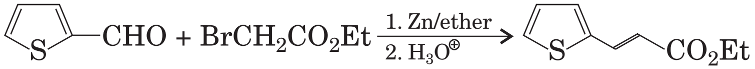
(iii) Citric acid can be prepared by this reaction.



Diethyl 2-oxobutanedioate

Citric acid

(iv) 2-Formylthiazole may be converted to the corresponding α,β-unsaturated ester by this reaction.

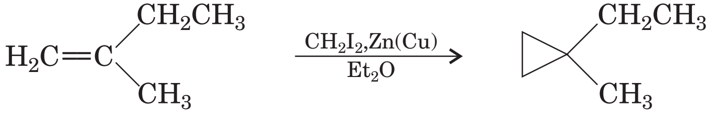


2.5.2.4 Simmons–Smith Reaction (Cyclopropanation of Alkenes)

A very useful organozinc compound is iodomethylzinc iodide (ICH_2ZnI). It reacts with olefins to form cyclopropane derivatives. This reaction is known as *Simmons–Smith reaction* and the organozinc compound, i.e., iodomethylzinc iodide is called *Simmons–Smith reagent* which is generated *in situ* and obtained by the following reaction similar to the formation of a Grignard reagent.

$$\underset{\text{Methylene di-iodide}}{CH_2I_2} + \underset{\text{Zinc–copper couple}}{Zn(Cu)} \xrightarrow{Et_2O} \underset{\text{Iodomethylzinc iodide}}{I{-}CH_2{-}ZnI}$$

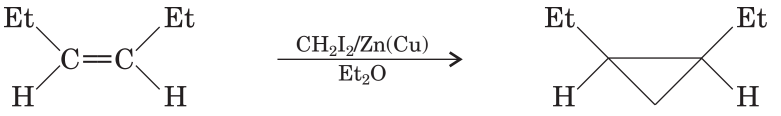
This kind of reagent is termed as carbenoid because it is not a free carbene ($:CH_2$) but has carbene like reactivity. An example of *Simmons–Smith* reaction is as follows:



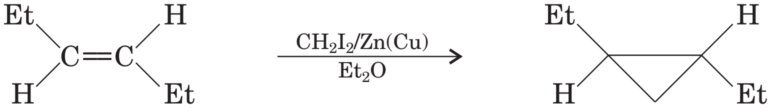
2-Methyl-1-butene

1-Ethyl-1-methylcyclopropane (79%)

The reaction is *stereospecific*. Substituents that were *cis* (or *trans*) in the alkene remain *cis* (or *trans*) in the cyclopropane. For example:

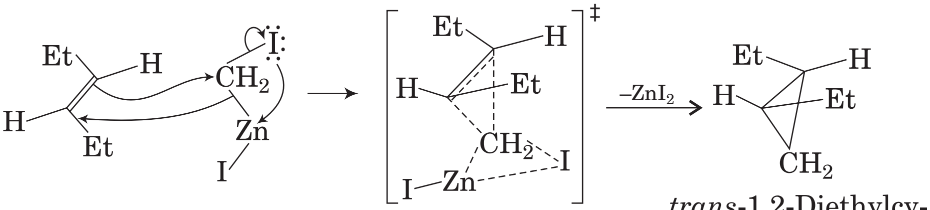


cis-3-Hexene *cis*-1,2-Diethylcyclopropane



trans-3-Hexene *trans*-1,2-Diethylcyclopropane

Mechanism of the reaction A concerted stereospecific transfer of methylene ($:CH_2$) from the carbenoid to the double bond of the alkene takes place to create a cyclopropane ring. This is a *syn*-addition process that takes place as follows:



T.S.

trans-1,2-Diethylcyclopropane

SOLVED PROBLEMS

1. **Which compound in each of the following pairs would you expect to have a more polar carbon—metal bond?**
   (a) $HC\equiv CMgBr$ or CH_3CH_2MgBr
   (b) Me_2Mg or Me_2Zn
   (c) $CH_3CH_2CH_2$ Li or $(CH_3CH_2CH_2)_3Al$

Solution

(a) Since C_{sp} is more electronegative than C_{sp3}, the C—Mg bond in $HC\equiv CMgBr$ is more polar than the C—Mg bond in CH_3CH_2MgBr.

(b) Since Zn is more electronegative (less electropositive) than Mg, the C—Mg bond in Me_2Mg is more polar than the C—Zn bond in Me_2Zn.

(c) Since Al is more electronegative (less electropositive) than Li, the C—Li bond in $CH_3CH_2CH_2Li$ is more polar than the C—Al bond in $(CH_3CH_2CH_2)_3Al$.

2. **Suggest appropriate methods for preparing each of the following organometallic compounds from the starting material of your choice:**
   (a) $CH_3CH_2CH_2CH_2MgI$ **(b)** $(CH_3)_2CHC\equiv CMgI$
   (c) $CH_3(CH_2)_4Li$ **(d)** $(CH_3CH_2CH_2CH_2)_2CuLi$

Solution

(a) $CH_3CH_2CH_2CH_2I + Mg \xrightarrow{\text{ether}} CH_2CH_2CH_2CH_2MgI$

1-Iodobutane — Butylmagnesium iodide

(b) $(CH_3)_2CHC{\equiv}CH + CH_3MgI \xrightarrow{-CH_4} (CH_3)_2CHC{\equiv}C\,MgI$

3-Methyl-1-butyne — Methylmagesium iodide — 3-Methylbutanylmagnesium iodide

(c) $CH_3CH_2CH_2CH_2CH_2Cl + 2Li \xrightarrow{Et_2O} CH_3CH_2CH_2CH_2CH_2Li + LiCl$

1-Chloropentane — Pentyllithium

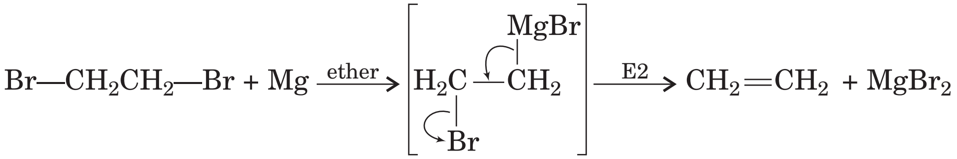
(d) $2CH_3CH_2CH_2CH_2Li + CuI \xrightarrow[\text{or } Et_2O]{\text{THF}} (CH_3CH_2CH_2CH_2)CuLi + LiI$

Butyllithium — Lithium dibutylcuprate

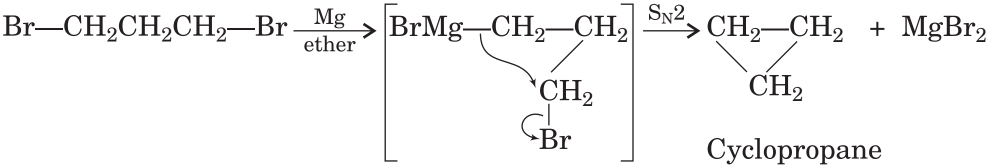
3. Predict the products expected to be formed when metallic magnesium is allowed to react with (a) $BrCH_2CH_2Br$, (b) $BrCH_2CH_2CH_2Br$ and (c) $BrCH_2CH_2CH_2CH_2Br$ in dry ether.

Solution

(a) The initially formed Grignard reagent eliminates (an E2 reaction) a molecule of $MgBr_2$ to form ethylene.



(b) The initially formed Grignard reagent undergoes intramolecular S_N2 reaction to form cyclopropane.



(c) 1,4-Dibromobutane reacts with metallic magnesium in dry ether to form a Grignard reagent and this is because formation of a cyclobutane ring is entropically less favoured.

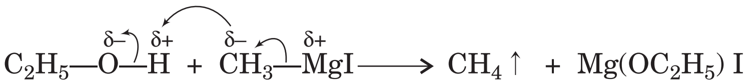
$$Br{-}CH_2CH_2CH_2CH_2{-}Br + Mg \xrightarrow{\text{ether}} BrMg\,CH_2CH_2CH_2CH_2MgBr$$

Grignard reagent

4. What do you mean by *Zerewitinoff active hydrogen determination*? Illustrate with a suitable example.

Solution The procedure for the determination of the number of active hydrogen atoms present in any compound using methylmagnesium iodide is known as Zerewitinoff active hydrogen determination.

In this procedure, the compound containing active hydrogen (hydrogen attached to an electronegative element like O, N, etc.) is allowed to react with methylmagnesium iodide (MeMgI) and the volume of the liberated methane is measured. If at NTP, the compound liberates 22.4 l of CH_4, it must contain one active hydrogen. For example:



$$C_2H_5\overset{\delta-}{—O}—\overset{\delta+}{H} + \overset{\delta-}{CH_3}—\overset{\delta+}{MgI} \longrightarrow CH_4\uparrow + Mg(OC_2H_5)\,I$$

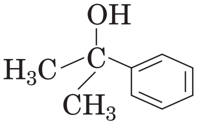
Ethanol (1 mol) 1 mol or 22.4 l (NTP)

Therefore, ethanol contains one active hydrogen.

5. **How would you plan a Grignard synthesis of an alcohol? Illustrate with an example.**

Solution Almost any alcohol can be synthesized by skilfully using a Grignard synthesis. In planning a Grignard synthesis the correct Grignard reagent and the correct aldehyde, ketone, ester or epoxide must be chosen. This can be done by examining the alcohol we want to synthesize and by giving special attention to the groups attached to the carbinol carbon, i.e., the carbon bearing the —OH group. Sometimes, the desired alcohol can be prepared by a number of ways. In such cases, the availability of starting compounds determines the actual way of carrying out the synthesis of that alcohol.

Suppose we want to prepare 2-phenyl-2-propanol. If we examine its structure, we will see that a phenyl group and two methyl groups are attached to the carbon atom bearing the —OH group.

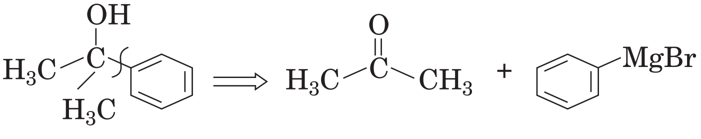


2-Phenyl-2-propanol

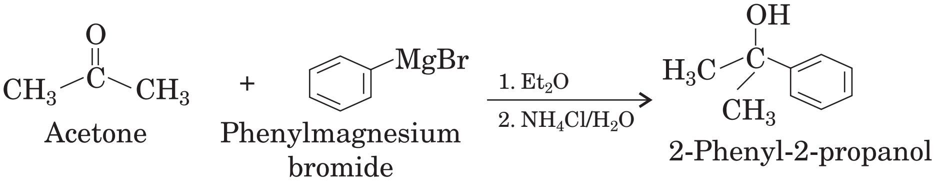
Therefore, this 3° alcohol can be synthesized in several different ways:

1. A ketone with two methyl groups (2-poropanone) may be allowed to react with phenylmagnesium bromide.

   Retrosynthetic analysis



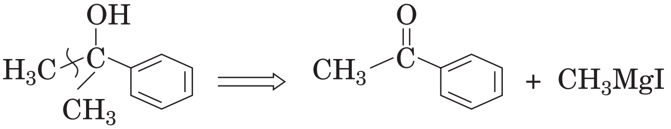
   Synthesis



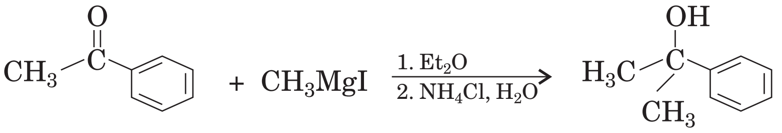
Acetone Phenylmagnesium bromide 2-Phenyl-2-propanol

2. A ketone containing a methyl and a phenyl group (acetophenone) may be allowed to react with methylmagnesium iodide.

Retrosynthetic analysis



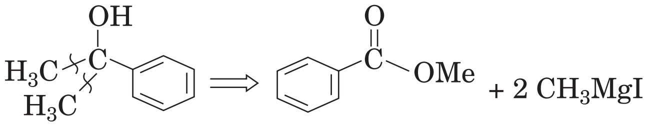
Synthesis



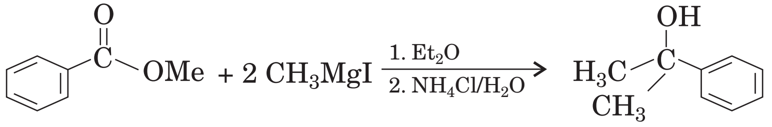
Acetophenone Methylmagnesium iodide 2-Phenyl-2-propanol

3. An ester of benzoic acid may be allowed to react with two molar equivalents of methylmagnesium iodide.

Retrosynthetic analysis



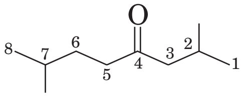
Synthesis



Methyl benzoate Methylmagnesium iodide 2-Phenyl-2-propanol

All these methods are expected to give the desired alcohol in good yields.

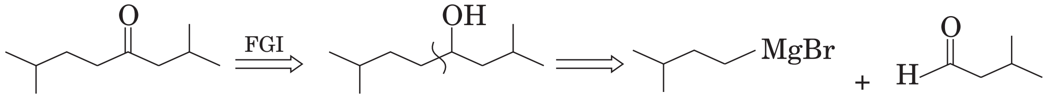
6. **Provide retrosynthetic analysis and synthesis of the following Ketone (an alcohol with no more than five carbon atoms is to be used as the only organic starting material).**



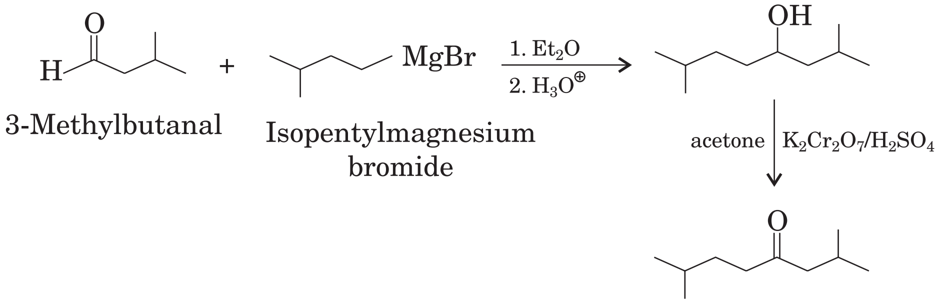
2,7-Dimethyl-4-octanone

Solution The carbon skeleton can be constructed from two five-carbon compounds using a Grignard reaction. The desired ketone can then be produced by oxidation of the resulting alcohol.

Retrosynthetic analysis



Synthesis

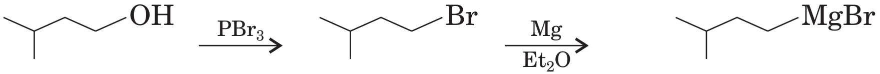


3-Methylbutanal

Isopentylmagnesium bromide

2,7-Dimethyl-4-octanone

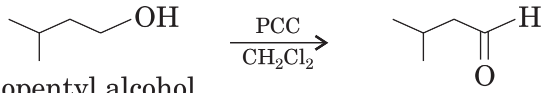
The required Grignard reagent and the aldehyde can be synthesized from isopentyl alcohol as follows:



Isopentyl alcohol

Isopentyl bromide

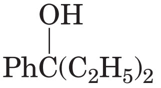
Isopentyl magnesium bromide



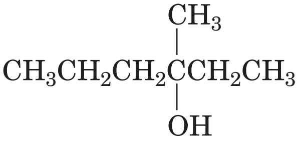
Isopentyl alcohol

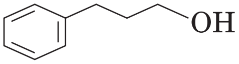
3-Methylbutanal

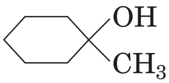
7. Provide retrosynthetic analysis and synthesis for each of the following alcohols, starting with appropriate alkyl or aryl halides.

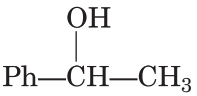
(a) 
$PhC(OH)(C_2H_5)_2$ (three ways)

(b) Ph_3COH (two ways)

(c) 
$CH_3CH_2CH_2C(CH_3)(OH)CH_2CH_3$ (three ways)

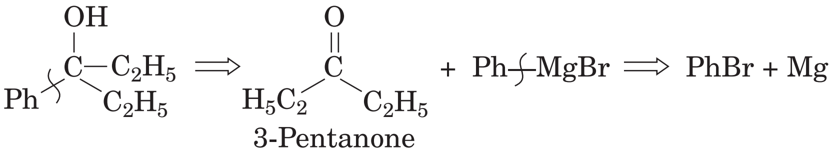
(d) 
(two ways)

(e) 
(three ways)

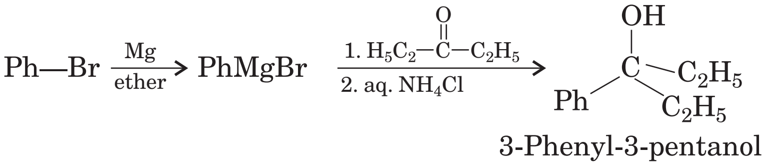
(f) 
$Ph—CH(OH)—CH_3$ (two ways)

Solution

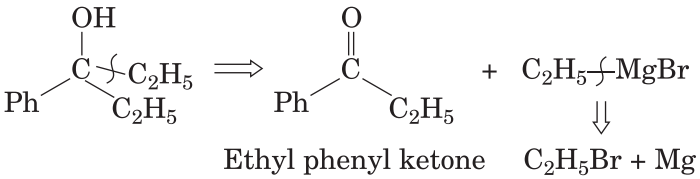
(a) (i) **Retrosynthetic analysis**



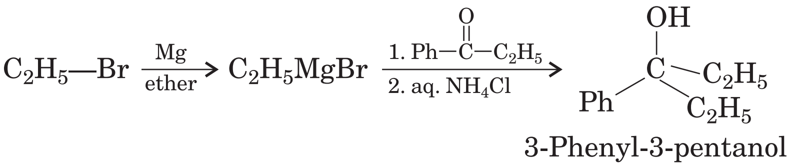
Synthesis



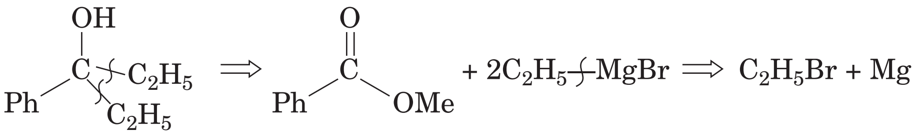
(ii) **Retrosynthetic analysis**



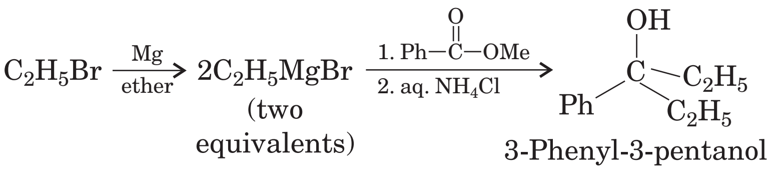
Synthesis



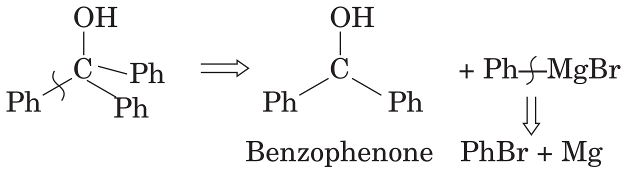
(iii) **Retrosynthetic analysis**



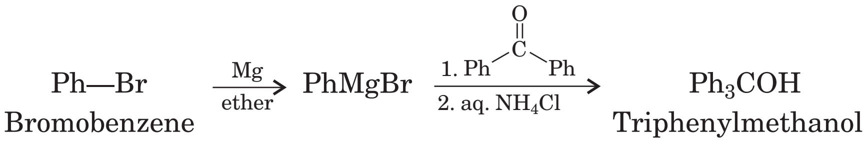
Synthesis



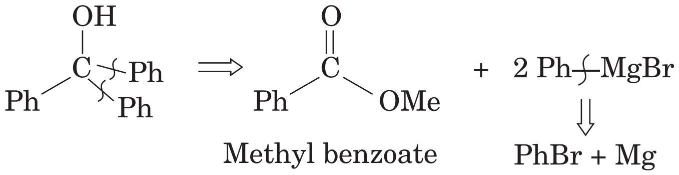
(b) (i) **Retrosynthetic analysis**



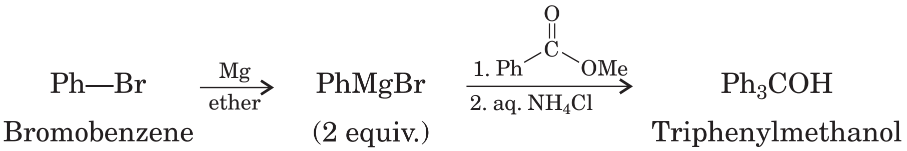
Synthesis



(ii) **Retrosynthetic analysis**

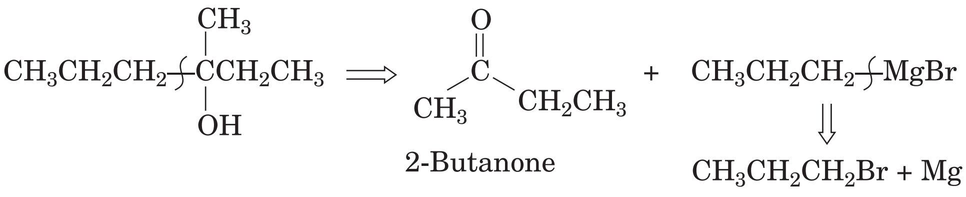


Synthesis

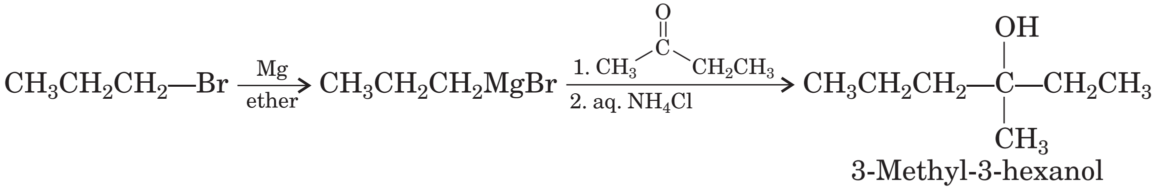


When a carbinol carbon contains two similar substituents, then it can be prepared by a Grignard synthesis involving an ester.

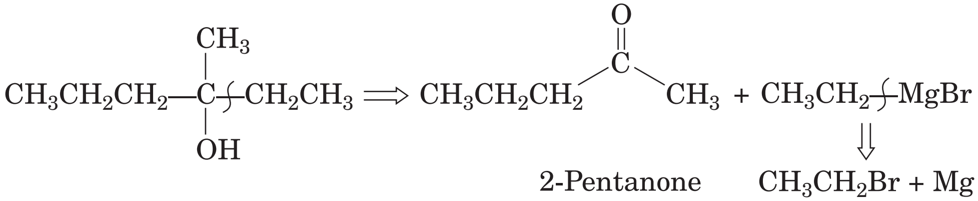
(c) (i) **Retrosynthetic analysis**



Synthesis



(ii) **Retrosynthetic analysis**

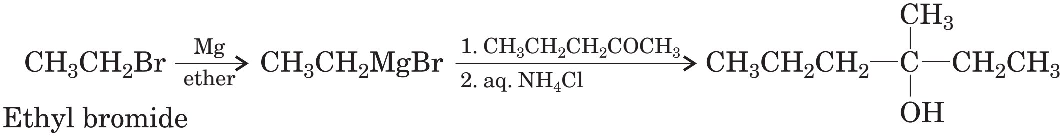


$$CH_3CH_2CH_2\text{—}\overset{CH_3}{\underset{OH}{C}}\text{—}CH_2CH_3 \Longrightarrow CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3 + CH_3CH_2\text{—}MgBr$$

$$CH_3CH_2MgBr \Longrightarrow CH_3CH_2Br + Mg$$

2-Pentanone

Synthesis

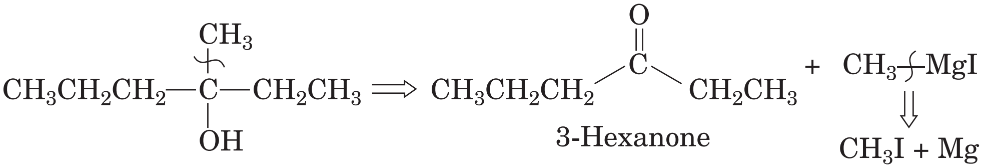


$$CH_3CH_2Br \xrightarrow[\text{ether}]{Mg} CH_3CH_2MgBr \xrightarrow[\text{2. aq. } NH_4Cl]{\text{1. } CH_3CH_2CH_2COCH_3} CH_3CH_2CH_2\text{—}\overset{CH_3}{\underset{OH}{C}}\text{—}CH_2CH_3$$

Ethyl bromide

3-Methyl-3-hexanol

(iii) **Retrosynthetic analysis**

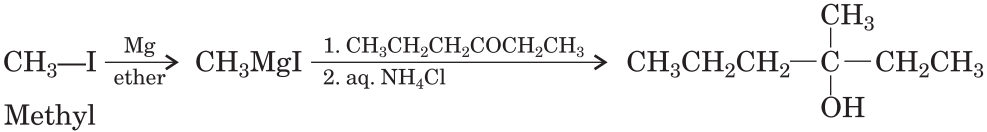


$$CH_3CH_2CH_2\text{—}\overset{CH_3}{\underset{OH}{C}}\text{—}CH_2CH_3 \Longrightarrow CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3 + CH_3\text{—}MgI$$

$$CH_3MgI \Longrightarrow CH_3I + Mg$$

3-Hexanone

Synthesis

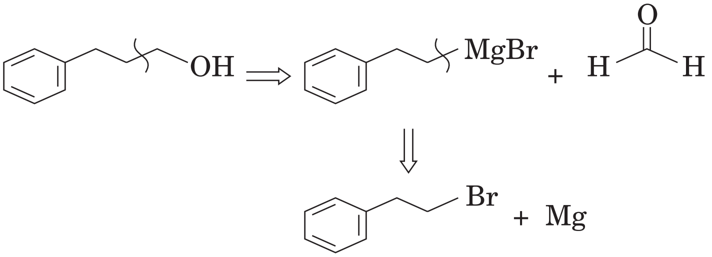


$$CH_3\text{—}I \xrightarrow[\text{ether}]{Mg} CH_3MgI \xrightarrow[\text{2. aq. } NH_4Cl]{\text{1. } CH_3CH_2CH_2COCH_2CH_3} CH_3CH_2CH_2\text{—}\overset{CH_3}{\underset{OH}{C}}\text{—}CH_2CH_3$$

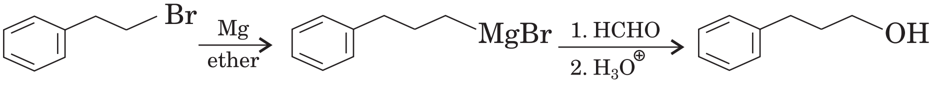
Methyl
iodide

3-Methyl-3-hexanol

(d) (i) **Retrosynthetic analysis**



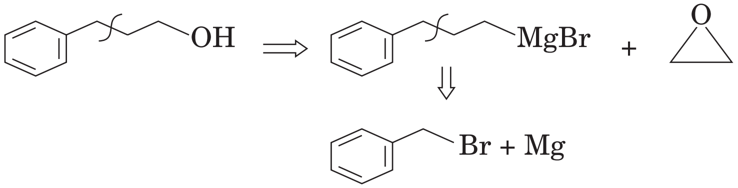
Synthesis



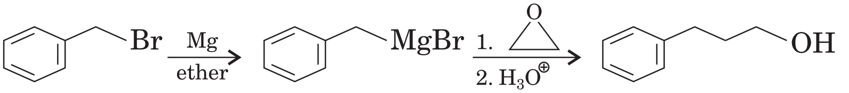
1-Bromo-2-phenyl-
ethane

3-Phenyl-1-propanol

(ii) **Retrosynthetic analysis**



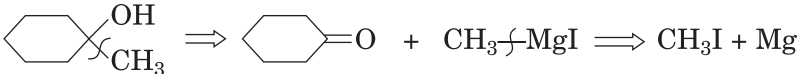
Synthesis



Benzyl bromide

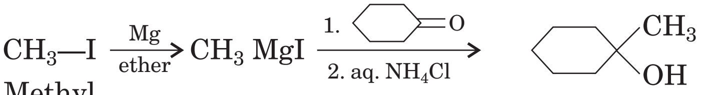
3-Phenyl-1-propanol

(e) (i) **Retrosynthetic analysis**



Cyclohexanone

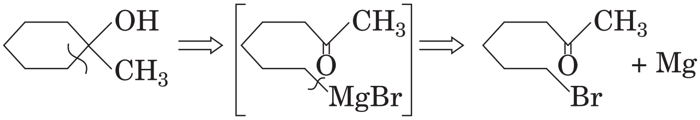
Synthesis



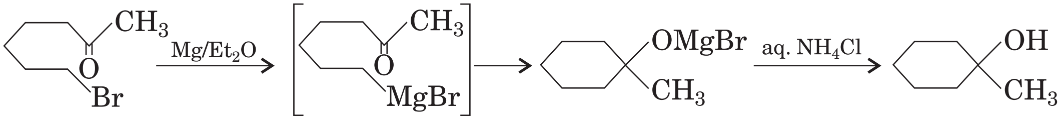
Methyl iodide

1-Methylcyclohexanol

(ii) **Retrosynthetic analysis**



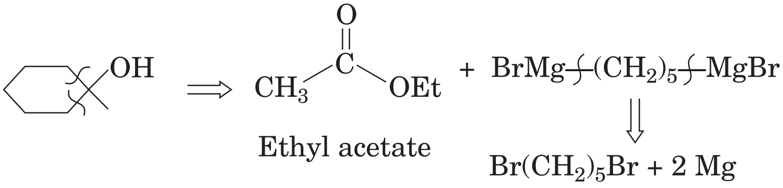
Synthesis



7-Bromo-2-heptanone

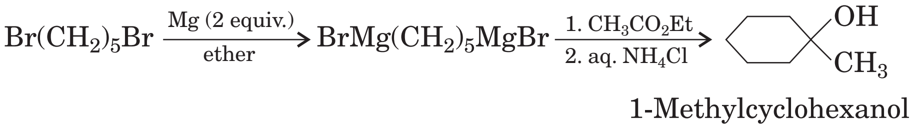
1-Methylcylohexanol

(iii) **Retrosynthetic analysis**

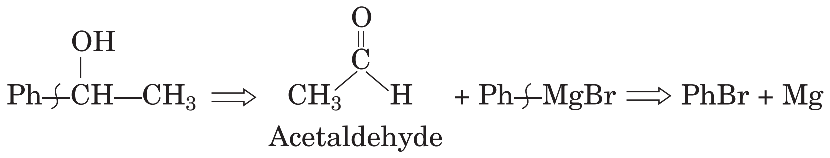


Ethyl acetate

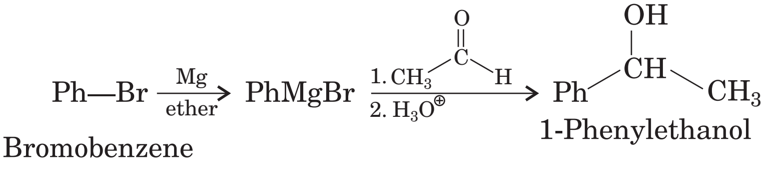
Synthesis



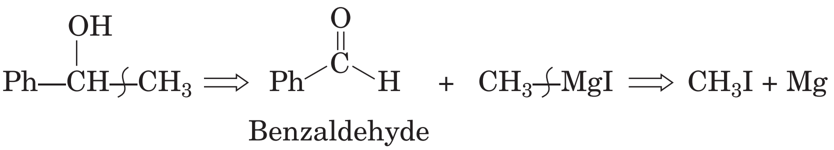
(f) (i) **Retrosynthetic analysis**



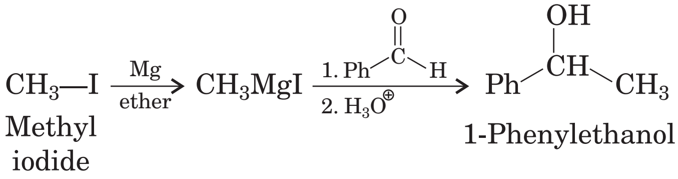
Synthesis



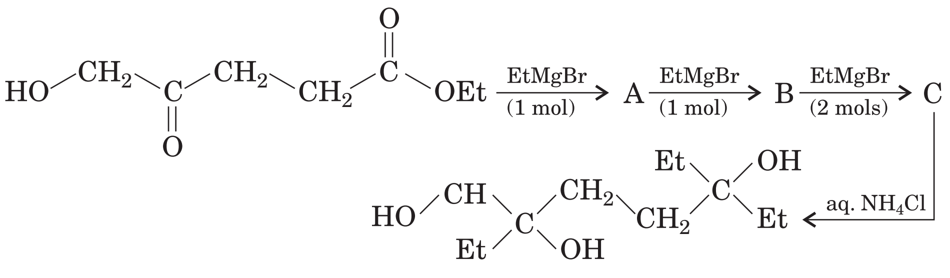
(ii) **Retrosynthetic analysis**



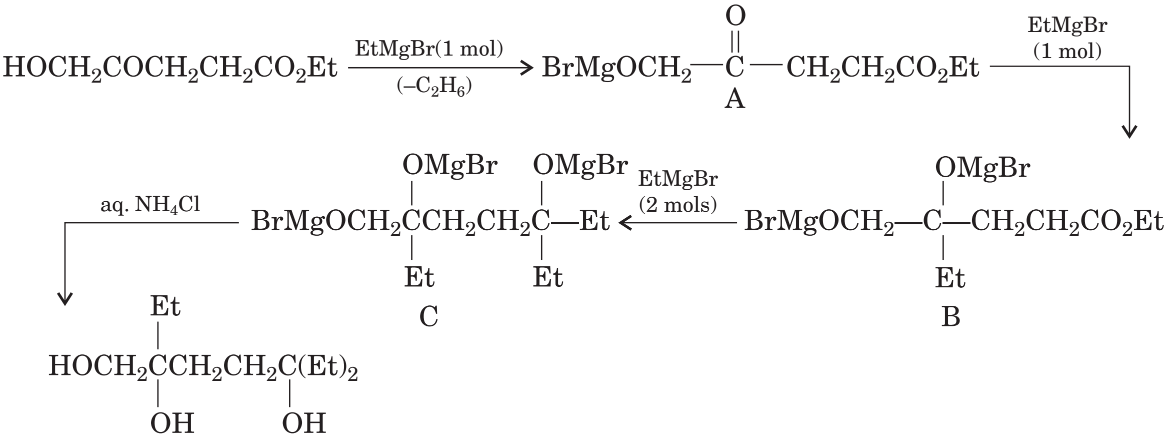
Synthesis



8. **Predict the intermediate products A, B and C in the following reaction sequence and give your reasoning.**



Solution The order of reactivity of various functional groups including active hydrogen towards Grignard reagent is as follows: active hydrogen >> —CHO >C=O > —COOR. Therefore, in the first step, EtMgBr reacts with the alcoholic —OH group to form A. In the next step, it reacts with the keto group to form B and in the final step, 2 mols of it reacts with the ester group to form C.

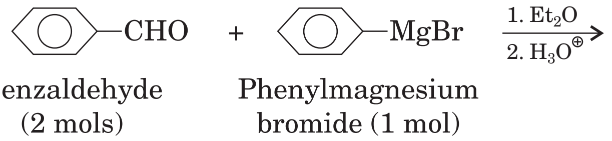


$$HOCH_2COCH_2CH_2CO_2Et \xrightarrow[(-C_2H_6)]{EtMgBr(1\ mol)} \underset{A}{BrMgOCH_2-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2CH_2CO_2Et}$$

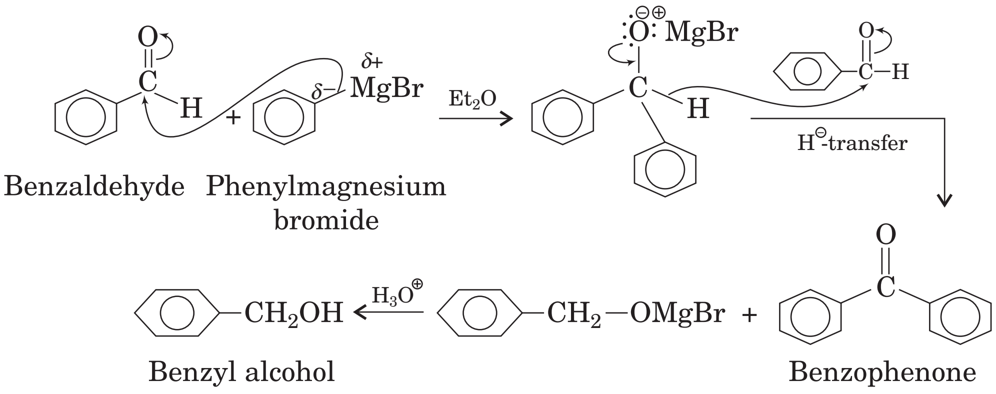
$$\xrightarrow{\substack{EtMgBr\\(1\ mol)}} \underset{B}{BrMgOCH_2-\overset{OMgBr}{\underset{Et}{C}}-CH_2CH_2CO_2Et} \xrightarrow[]{\substack{EtMgBr\\(2\ mols)}} \underset{C}{BrMgOCH_2\overset{OMgBr}{\underset{Et}{C}}CH_2CH_2\overset{OMgBr}{\underset{Et}{C}}-Et}$$

$$\xrightarrow{aq.\ NH_4Cl} HOCH_2\overset{Et}{\underset{OH}{C}}CH_2CH_2\underset{OH}{C}(Et)_2$$

9. **Predict the products expected to be formed in the following reaction and give your reasoning:**



Solution Phenylmagnesium bromide reacts with two molar equivalents of benzaldehyde to yield benzophenone (a ketone) and benzyl alcohol (a 1° alcohol) by a hydride transfer mechanism (as in *Cannizzaro reaction*).



10. How would you convert an alcohol (ROH) to its higher homologue (RCH_2OH) by using a Grignard reaction in one of the steps?

Solution

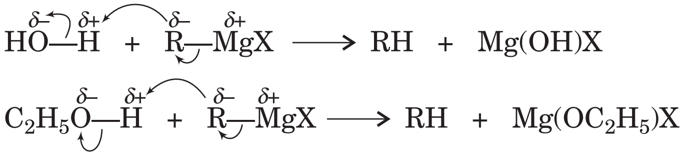
$$R{-}OH \xrightarrow[\text{or } NaBr/H_2SO_4]{HBr} RBr \xrightarrow[\text{ether}]{Mg} RMgBr \xrightarrow[\text{ether}]{HCHO} RCH_2OMgBr \xrightarrow{H_3O^{\oplus}} RCH_2OH$$

11. Explain why alkyl fluorides (R—F) do not produce Grignard reagents with metallic magnesium in dry ether medium.

Solution The C—F bond is much stronger than the other C—X (X = Cl, Br, I) bonds. Therefore, homolytic cleavage of the C—F bond is quite difficult and as a consequence, alkyl fluorides do not produce Grignard reagents when allowed to react with magnesium. (Bond dissociation energies for C—F = 107 kcal/mol; C—Cl = 78 kcal/mol; C—Br = 68 kcal/mol and C—I = 51 kcal/mol).

12. The solvent ether used in the preparation of Grignard reagents must be scrupulously dry and free from alcohol. Give reasons.

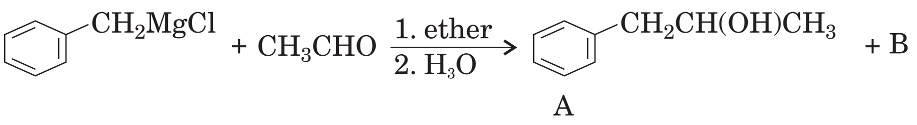
Solution Compounds containing active hydrogen such as H_2O or C_2H_5OH react extremely rapidly with Grignard reagent producing hydrocarbon. So, the Grignard reagent will not be obtained as such. For this reason, ether used as solvent in the preparation of Grignard reagent must be scrupulously dry and alcohol-free.



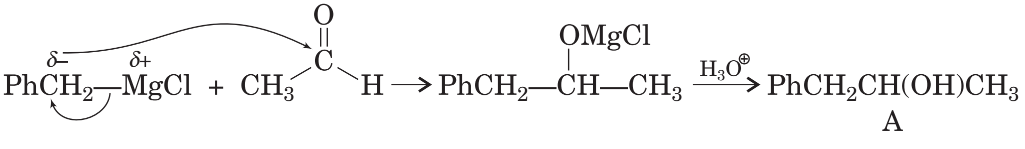
$$H\overset{\delta-}{O}{-}\overset{\delta+}{H} + \overset{\delta-}{R}{-}\overset{\delta+}{Mg}X \longrightarrow RH + Mg(OH)X$$

$$C_2H_5\overset{\delta-}{O}{-}\overset{\delta+}{H} + \overset{\delta-}{R}{-}\overset{\delta+}{Mg}X \longrightarrow RH + Mg(OC_2H_5)X$$

13. Identify the product B in the following reaction. The compound B is isomeric with the compound A and reacts with I_2/NaOH to form iodoform and the sodium salt of a carboxylic acid having neutralisation equivalent 136.

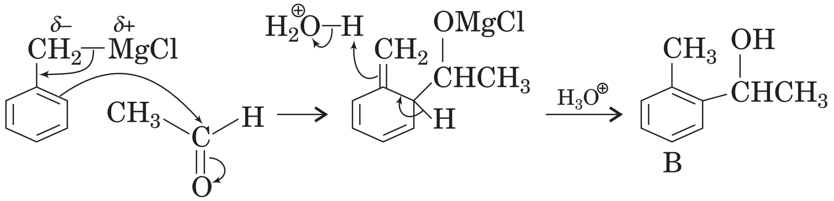


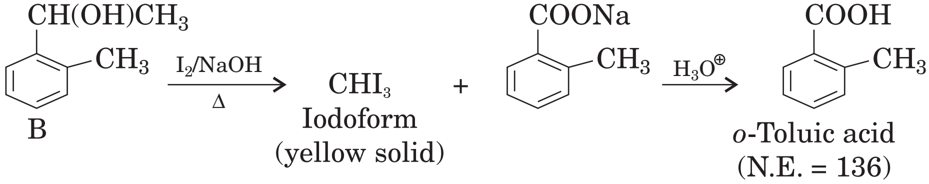
Solution The compound A is formed by a normal Grignard reaction:



$$Ph\overset{\delta-}{C}H_2{-}\overset{\delta+}{Mg}Cl + CH_3{-}\overset{O}{\overset{\|}{C}}{-}H \longrightarrow PhCH_2{-}\overset{OMgCl}{\overset{|}{C}H}{-}CH_3 \xrightarrow{H_3O^{\oplus}} \underset{A}{PhCH_2CH(OH)CH_3}$$

Since the compound B is found to respond iodoform test, it must contain a —CH(OH)CH_3 group and there must be a —CH_3 group at the *ortho*-position. This compound is produced by an abnormal Grignard reaction such as follows:





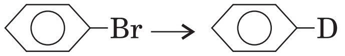
14. How would you convert?

(a) $\overset{*}{C}O_2 \longrightarrow CH_3\overset{*}{C}OOH\ [\overset{*}{C}={}^{14}C]$

(b) $\overset{*}{C}O_2 \longrightarrow \overset{*}{C}H_3COOH$

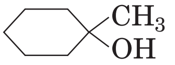
(c) $\overset{*}{C}O_2 \longrightarrow \overset{*}{C}H_3\overset{*}{C}OOH$

(d)



(e) $CH_3CH_2CH_2CH_3 \longrightarrow CH_3CHDCH_2CH_3$

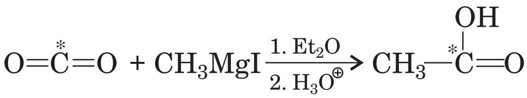
(f) $Br(CH_2)_3Br \longrightarrow$



(g) $CH_3(CH_2)_3CH_2Br \longrightarrow CH_3(CH_2)_5CH_2Br$

Solution

(a)



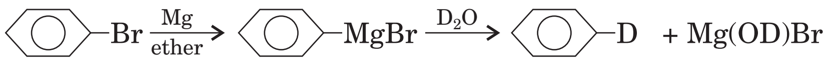
$$O=\overset{*}{C}=O + CH_3MgI \xrightarrow[2.\ H_3O^{\oplus}]{1.\ Et_2O} CH_3-\overset{\overset{\large OH}{|}}{\overset{*}{C}}=O$$

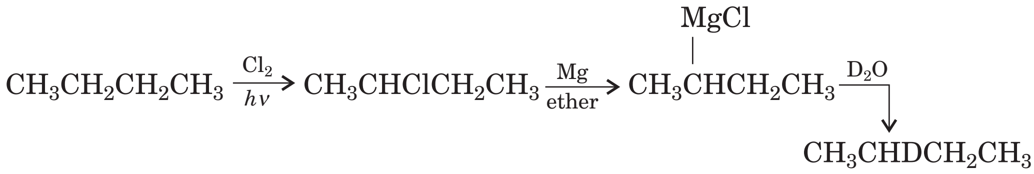
(b) $$O=\overset{*}{C}=O + 3H_2 \xrightarrow{\text{Catalyst}} H_2O + \overset{*}{C}H_3OH \xrightarrow[\text{red P}]{I_2} \overset{*}{C}H_3I \xrightarrow[\text{ether}]{\text{Mg}} \overset{*}{C}H_3MgI$$

$$\overset{*}{C}H_3COOH \xleftarrow[2.\ H_3O^{\oplus}]{1.\ CO_2} \overset{*}{C}H_3MgI$$

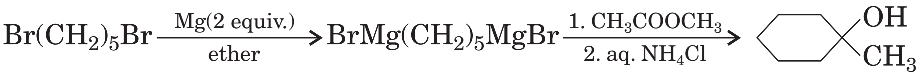
(c) It $\overset{*}{C}O_2$ is used in the final step of (b), $\overset{*}{C}O_3\overset{*}{C}OOH$ will be obtained.

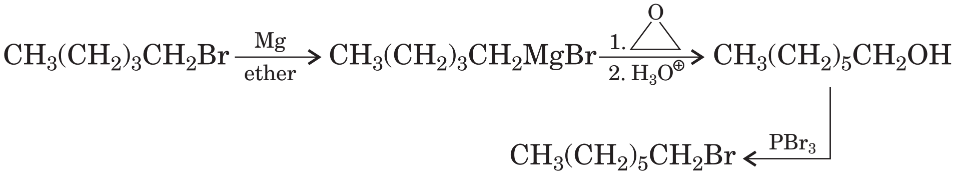
(d)



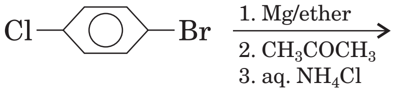
(e) 

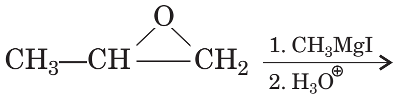
$$CH_3CH_2CH_2CH_3 \xrightarrow[h\nu]{Cl_2} CH_3CHClCH_2CH_3 \xrightarrow[ether]{Mg} CH_3\overset{\overset{MgCl}{|}}{C}HCH_2CH_3 \xrightarrow{D_2O} CH_3CHDCH_2CH_3$$

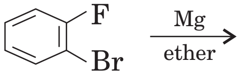
(f) 

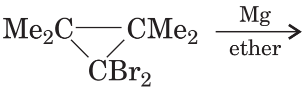
(g) 

15. Predict the product and suggest a mechanism for each of the following reactions:

(a) 

(b) 

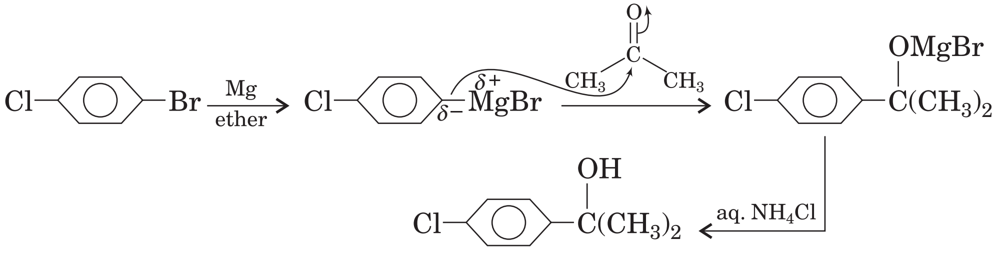
(c) 

(d) 

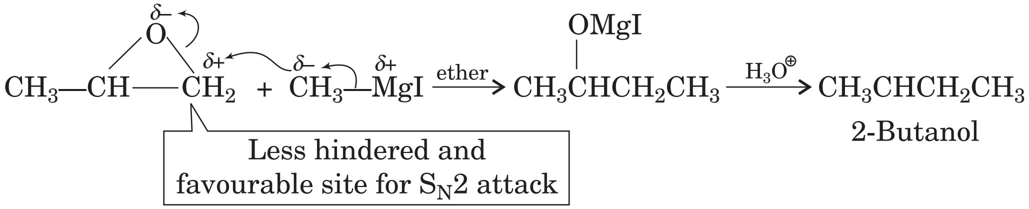
(e) $Br(CH_2)_4COCH_3 \xrightarrow[2.\ aq.\ NH_4Cl]{1.\ Mg/ether}$

Solution

(a) Since C—Br bond is weaker than the C—Cl bond, *p*-chlorobromobenzene reacts with magnesium in dry ether to yield *p*-chlorophenylmagnesium bromide. This reacts with acetone to form a tertiary alcohol.



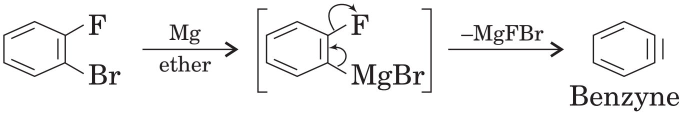
(b) The epoxide undergoes nucleophilic attack (S_N2) at the less hindered methylene carbon by $\overset{\ominus}{C}H_3$ from CH_3MgI to yield a secondary alcohol.



Less hindered and favourable site for S_N2 attack

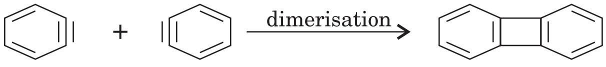
2-Butanol

(c) *o*-Fluorobromobenzene reacts with magnesium to form *o*-fluorophenylmagnesium bromide which readily eliminates a molecule of MgFBr to produce the unstable intermediate benzyne. Benzyne then dimerizes to given biphenylene.



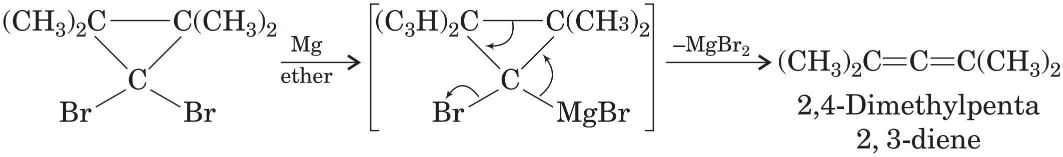
Benzyne

Now,

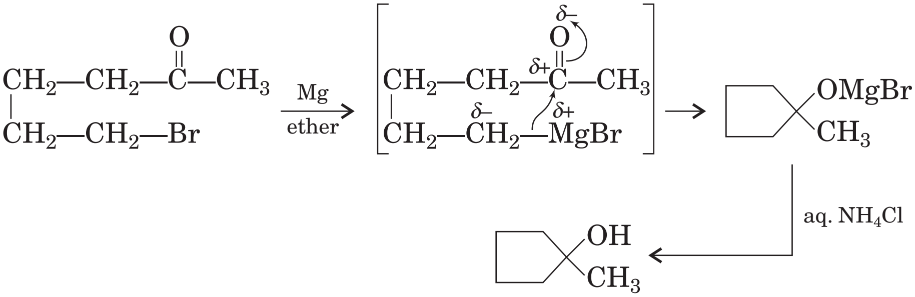


Biphenylene

(d) The cyclopropane derivative reacts with magnesium to form a Grignard reagent which readily eliminates a molecule of $MgBr_2$ to form 2,4-dimethylpenta-2,3-diene.



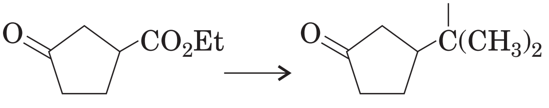
(e) The bromoketone reacts with magnesium to form a Grignard reagent which readily reacts with the $\rangle C=O$ group to yield 1-methylcyclopentanol.



1-Methylcyclopentanol

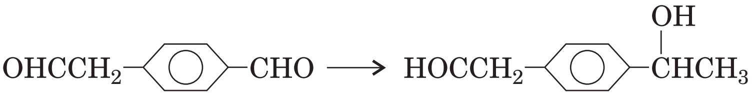
16. How would you carry out the following transformations?

(a)

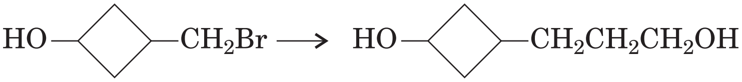


(b) $CH_3COCH_2CH_2CH_2Br \longrightarrow CH_3COCH_2CH_2CH(OH)CH_3$

(c)

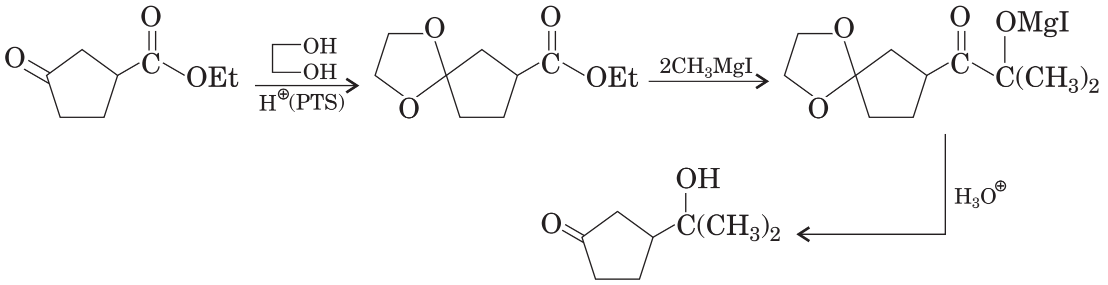


(d)

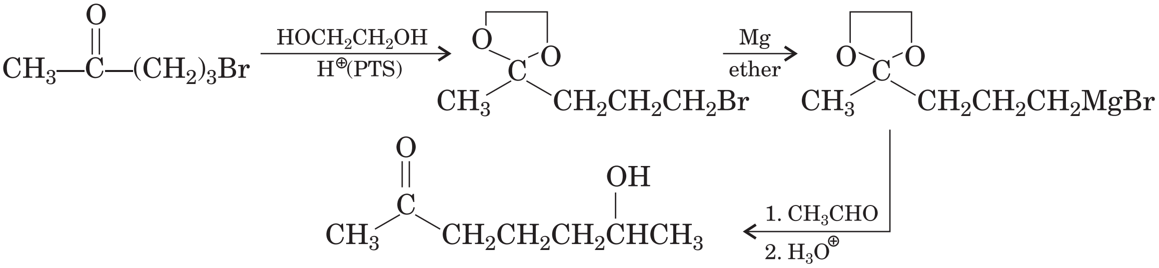


Solution

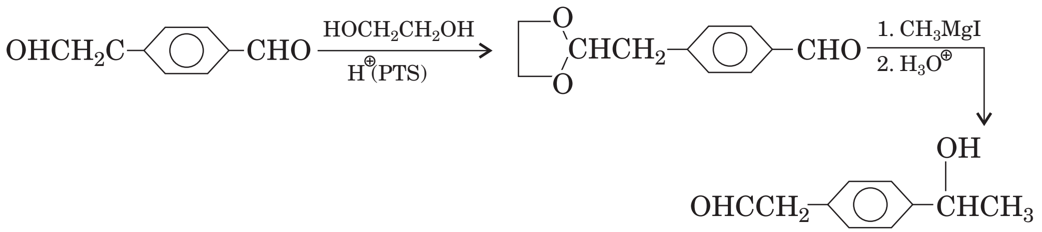
(a) Since a Grignard reagent reacts with both the keto and ester functional groups, the former group is to be protected by acetal formation. The carbonyl protected ester is then allowed to react with two molar equivalents of CH_3MgI to give, after acidification, the desired tertiary alcohol. The acetal undergoes ready hydrolysis in the presence of dilute acid.



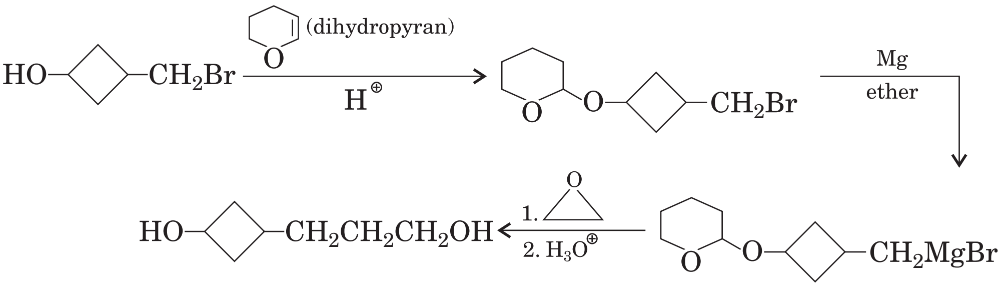
(b) The carbonyl group of the compound is to be protected because if the bromoketone is allowed to react with magnesium, the resulting Grignard reagent reacts intramolecularly with the C=O group to give a cyclic product. Therefore, this transformation may be carried out as follows:



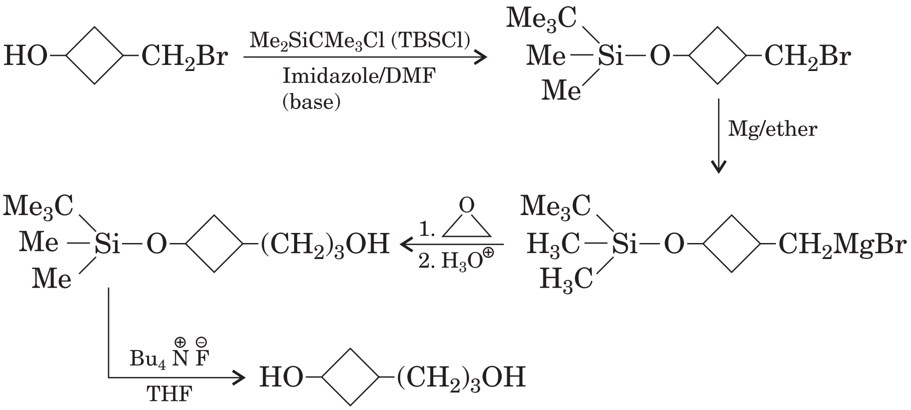
(c) There are two —CHO groups in the compound. But their reactivities are different. The —CHO group directly attached to the ring is relatively less reactive due to resonance. Taking this advantage of differential reactivity, the more reactive —CHO group which is not directly attached to the ring can be protected by acetal formation. The transformation may be carried out as follows:



(d) The —OH group is to be protected before preparation of the Grignard reagent from the starting bromide and this is because the resulting Grignard will readily react with the active hydrogen and will be decomposed. Thus, this transformation is to be carried out as follows:



The tetrahydropyranyl ether moiety also undergoes hydrolysis in the presence of dilute acid. The alcohol hydroxyl group can also be protected by converting it to a *tert*-butyldimethylsilyl (TBS) ether. After conducting the Grignard reaction, the original alcohol group can be liberated by cleavage of the silyl ether with fluoride ion.



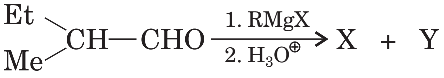
17. Using $CH_3CH_2C{\equiv}CH$ and $BrCH_2CH_2CHO$ devise a synthesis of $CH_3CH_2C{\equiv}CCH_2CH_2CHO$ (use other reagents you need).

Solution $CH_3CH_2C{\equiv}CH \xrightarrow{CH_3MgI} CH_4\uparrow + CH_3CH_2C{\equiv}CMgI$

$BrCH_2CH_2CHO \xrightarrow[H^{\oplus}]{2EtOH} BrCH_2CH_2CH(OEt)_2$ (—CHO group is protected)

Then, $CH_3CH_2C{\equiv}CMgI + BrCH_2CH_2CH(OEt)_2 \xrightarrow[-MgIBr]{S_N2} CH_3CH_2C{\equiv}CCH_2CH_2CH(OEt)_2$

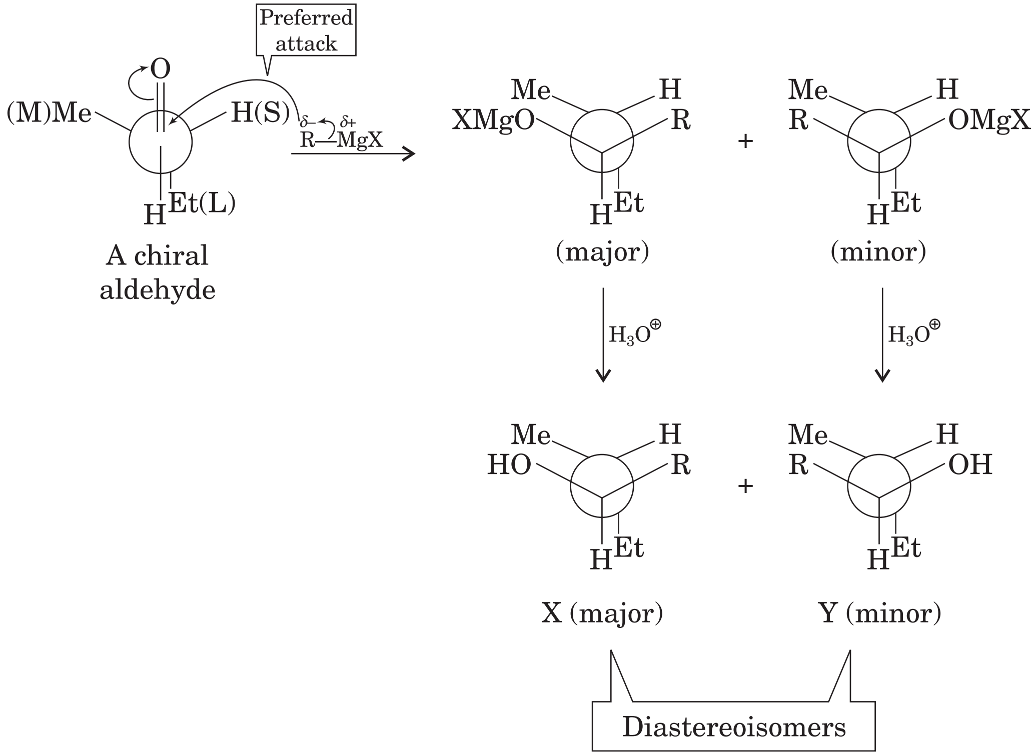
$\xrightarrow{H_3O^{\oplus}\text{ (deprotection)}} CH_3CH_2C{\equiv}CCH_2CH_2CHO$

18. 

$\begin{matrix}Et \\ Me\end{matrix}\!\!>CH{-}CHO \xrightarrow[2.\ H_3O^{\oplus}]{1.\ RMgX} X + Y$

Predict whether X or Y predominates. Give your reasoning.

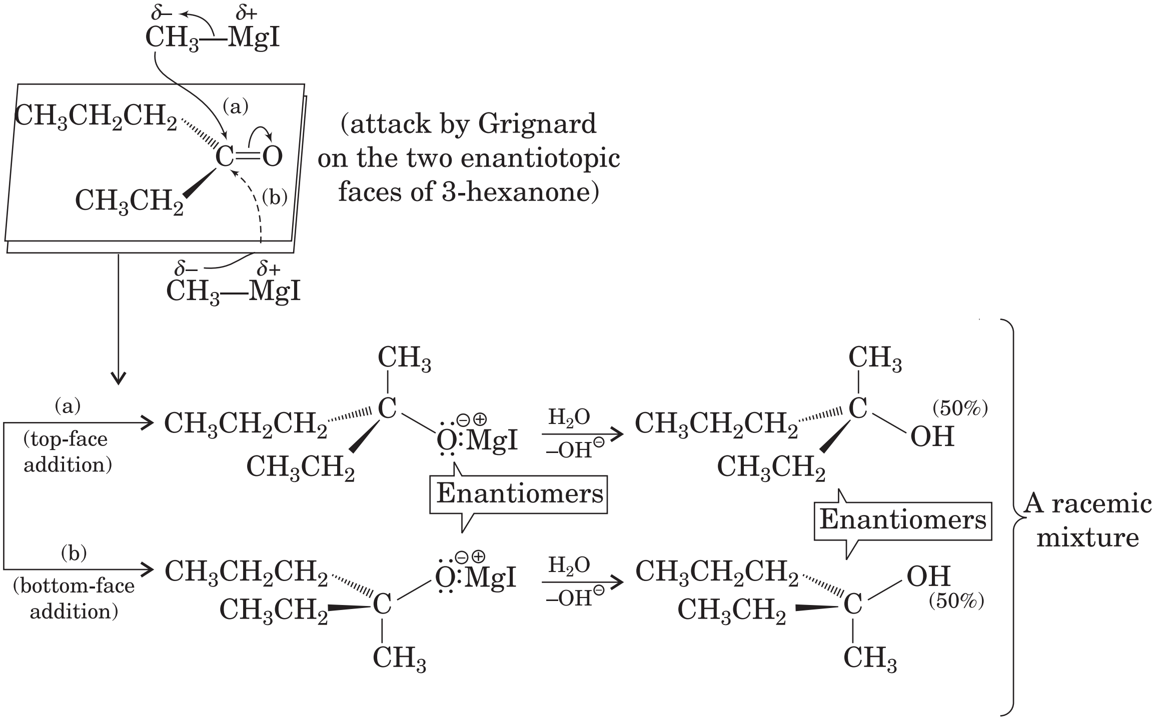
Solution Since the group attached to the —CHO group in the aldehyde is chiral, the environments of addition from the two faces of the C═O group are no longer equivalent and attacks from above and below are not therefore sterically equally likely. As a result, the products will not also be formed in equal amounts. In such a case *Cram's rule* predicts the predominant addition product. The rule which considers only steric effect, states that a carbonyl compound will react in that conformation in which the O atom of the C═O group orients itself *anti* to the largest of the three substituents on the α–C atom and the nucleophite will attack the carbonyl carbon atom preferentially from the side of the small group (S), i.e., from the least hindered side (involving a low energy T.S.) to give the major product.



19. Predict the stereochemical outcome of the following reaction and give your reasoning:

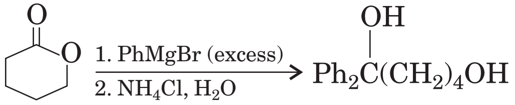
$$\mathbf{CH_3CH_2COCH_2CH_2CH_3 \xrightarrow[2.\ H_2O]{1.\ CH_3MgI}}$$

Solution The Grignard reagent adds from both sides of the trigonal planar carbonyl group with equal facility to give two alkoxides, each containing a new stereogenic centre. Protonation with water yields a mixture of equal amounts of two enantiomers, i.e., a racemic mixture.

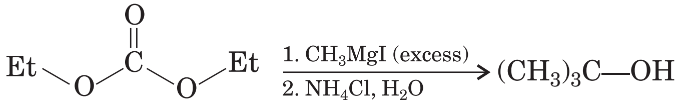


20. Suggest a mechanism for each of the following reactions:

(a)

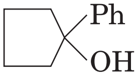


(b)



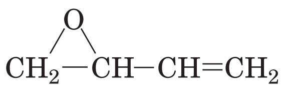
$$\text{Et}-\text{O}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{O}-\text{Et}\xrightarrow[\text{2. NH}_4\text{Cl, H}_2\text{O}]{\text{1. CH}_3\text{MgI (excess)}}(\text{CH}_3)_3\text{C—OH}$$

(c) $\text{BrMgCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{MgBr} + \text{PhCO}_2\text{Me} \xrightarrow[\textbf{2. aq. NH}_4\textbf{Cl}]{\textbf{1. ether}}$



(d) $\text{CH}_2{=}\text{C}{=}\text{O} + \text{EtMgBr} \xrightarrow[\textbf{2. H}_3\textbf{O}^{\oplus}]{\textbf{1. ether}} \text{C}_2\text{H}_5\text{COCH}_3$

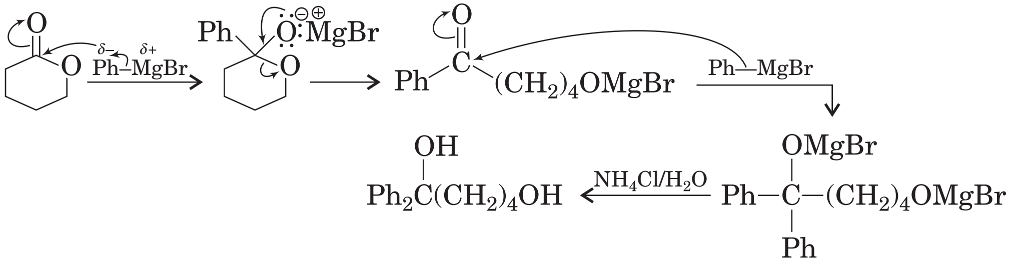
(e)

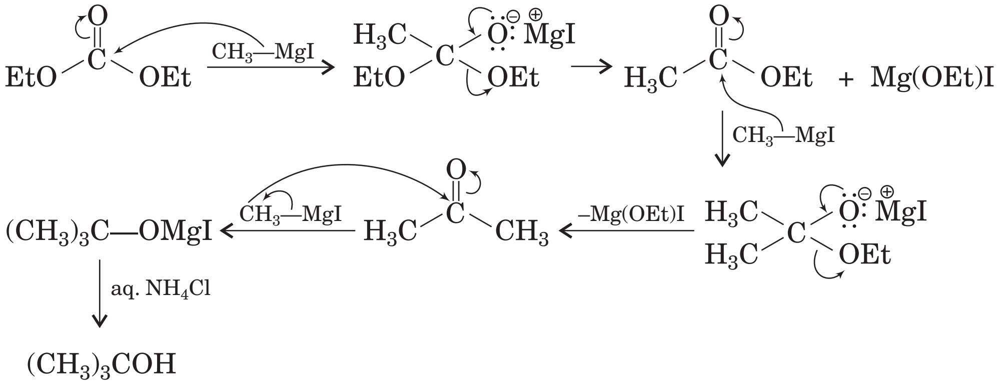


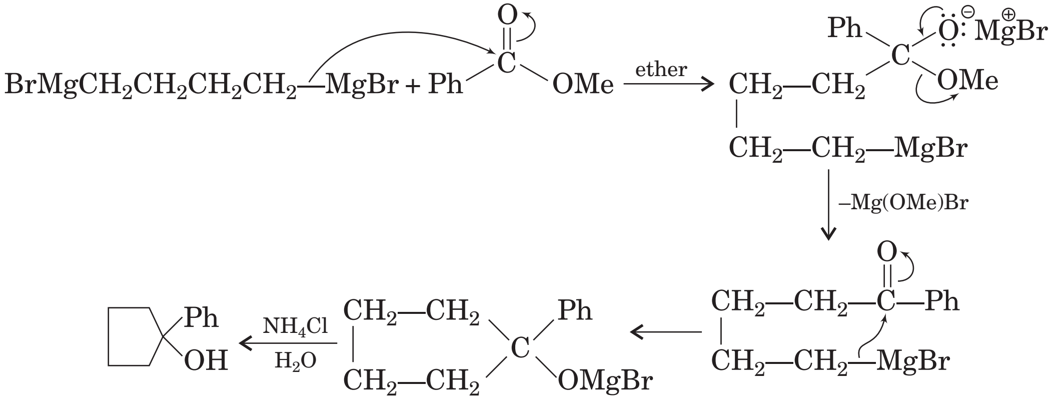
$+ \text{C}_2\text{H}_5\text{MgBr} \xrightarrow[\text{2. H}_3\text{O}^{\oplus}]{\text{1. ether}} \text{HOCH}_2\text{CH}{=}\text{CHCH}_2\text{CH}_2\text{CH}_3$

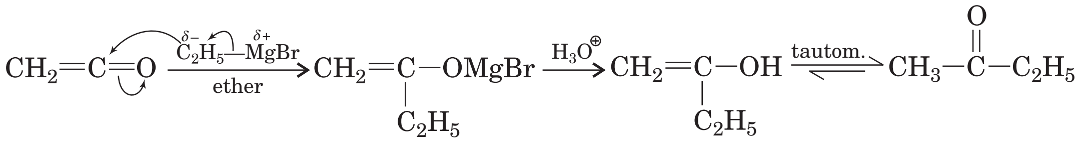
Solution

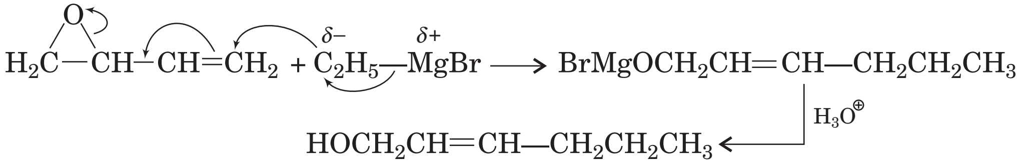
(a)

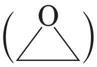
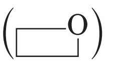


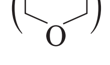
(b) 

(c) 

(d) 

(e) 

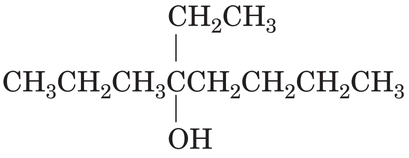
21. Ethylene oxide () and trimethylene oxide () react readily with a Grignard reagent. However, a Grignard reagent does not react with THF for which it is used as a solvent in Grignard Synthesis. Explain these observations.

Solution The three- and four-membered rings are very strained, and thus, they open on reaction with a Grignard reagent (RMgX). THF or tetrahydrofuran () possesses an essentially unstrained ring, and hence, it is far more resistant to attack by a Grignard reagent.

22. Analyse the following structures and then determine all the practical combination of Grignard reagent and carbonyl compound that will give rise to each:

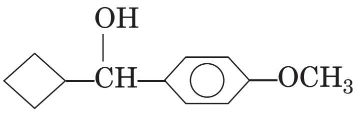
(a) $(CH_3)_3CCH_2OH$

(b)



$$CH_3CH_2CH_3\underset{\displaystyle OH}{\overset{\displaystyle CH_2CH_3}{C}}CH_2CH_2CH_2CH_3$$

(c)



(d) $CH_3CH_2CH(OH)CH_2CH_2CH(CH_3)_2$

Solution

(a) $(CH_3)_3$ CMgCl + HCHO (only one combination)

(b) **Three combinations:**

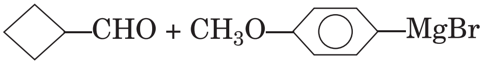
(i) $CH_3CH_2CH_2COCH_2CH_2CH_2CH_3 + CH_3CH_2MgBr$

(ii) $CH_3CH_2COCH_2CH_2CH_2CH_3 + CH_3CH_2CH_2MgBr$

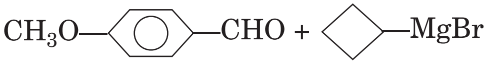
(iii) $CH_3CH_2CH_2COCH_2CH_3 + CH_3CH_2CH_2CH_2MgBr$

(c) **Two combinations:**

(i)



(ii)



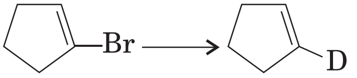
(d) **Two combinations:**

(i) $CH_3CH_2CHO + (CH_3)_2CHCH_2CH_2MgBr$

(ii) $(CH_3)_2CHCH_2CH_2CHO + CH_3CH_2MgBr$

23. How would you carry out the following transformations?

(a)

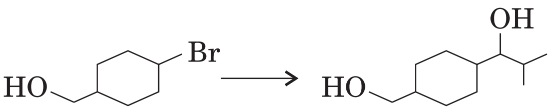


(b) $Me_3CCl \longrightarrow Me_3\ C—CN$

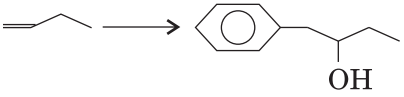
(c) $PhBr \longrightarrow PhCH_2CHO$

(d) $HC{\equiv}CH \longrightarrow HO_2C—C{\equiv}C—CO_2H$

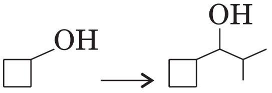
(e)



(f)

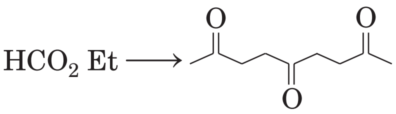


(g)

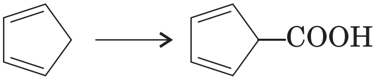


(h) $(CH_2)_5Br_2 \longrightarrow (CH_2)_5(NH_2)_2$

(i)

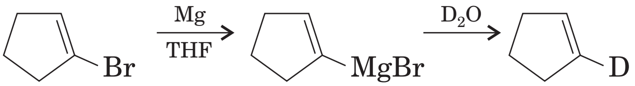


(j)



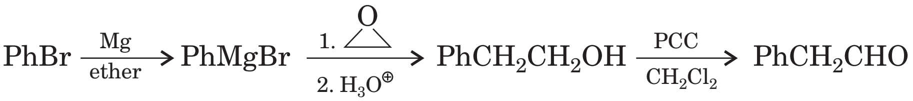
Solution

(a)



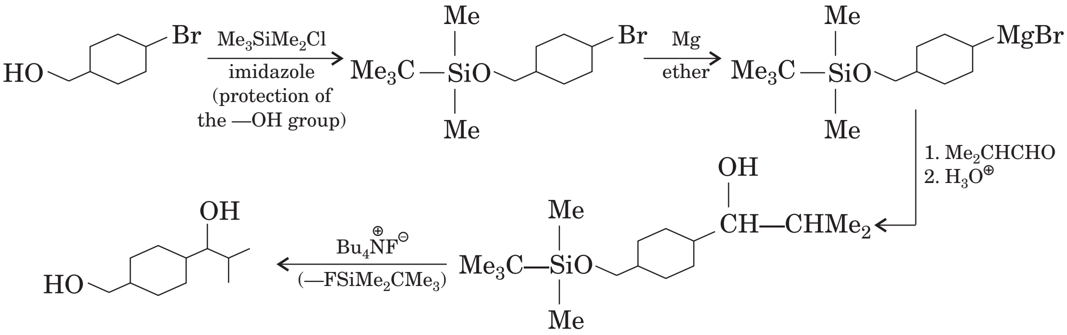
(b) $Me_3CCl \xrightarrow[\text{ether}]{\text{Mg}} Me_3CMgCl \xrightarrow{\text{ClCN}} (CH_3)_3C\text{—}CN + MgCl_2$

(c)

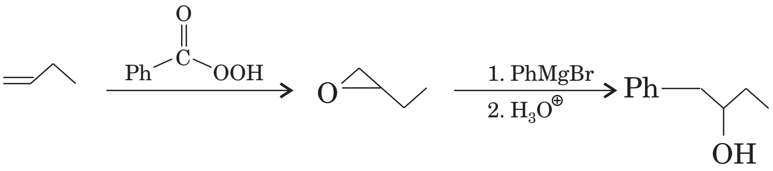


(d) $HC{\equiv}CH \xrightarrow[\text{—}2CH_4]{CH_3MgI\ (2\ \text{equiv.})} BrMg\,C{\equiv}C\,MgBr \xrightarrow[2.\ H_3O^{\oplus}]{1.\ CO_2\ (2\ \text{equiv.})} HO_2C\text{—}C{\equiv}C\text{—}CO_2H$

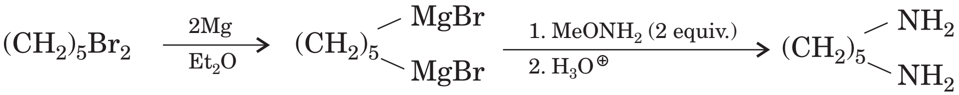
(e)



(f)

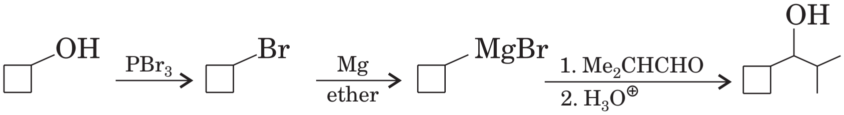


(g)

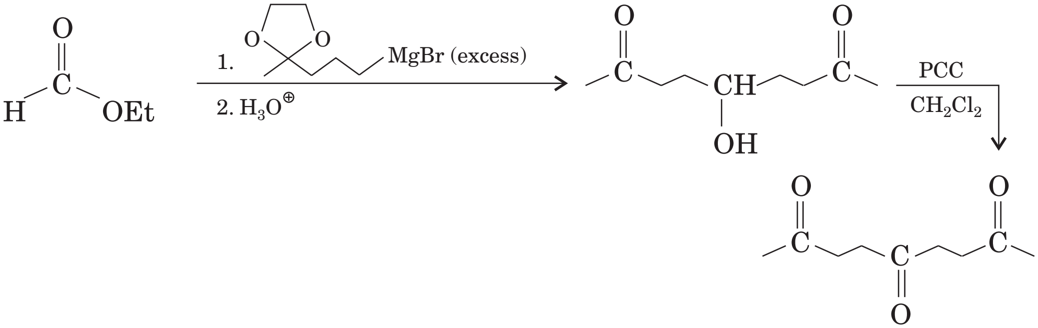


$$(CH_2)_5Br_2 \xrightarrow[Et_2O]{2Mg} (CH_2)_5\begin{matrix}MgBr\\MgBr\end{matrix} \xrightarrow[2.\ H_3O^{\oplus}]{1.\ MeONH_2\ (2\ \text{equiv.})} (CH_2)_5\begin{matrix}NH_2\\NH_2\end{matrix}$$

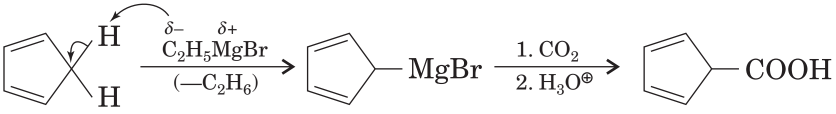
(h)



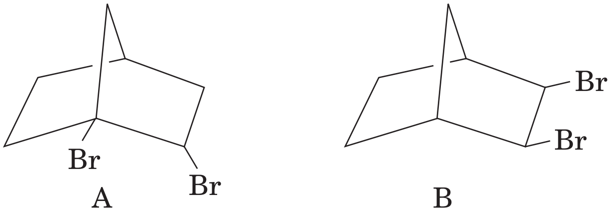
(i)



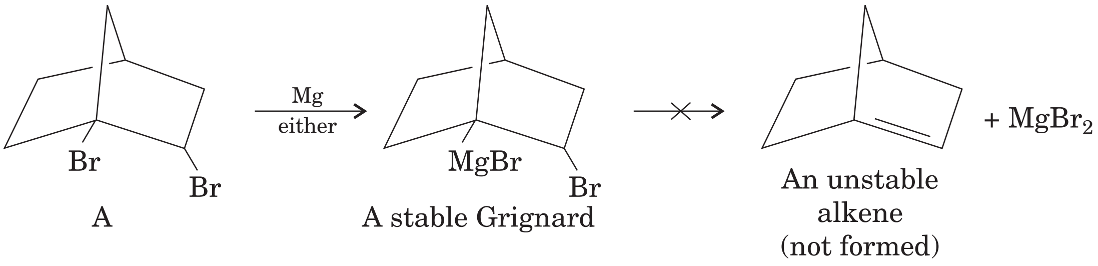
(j)



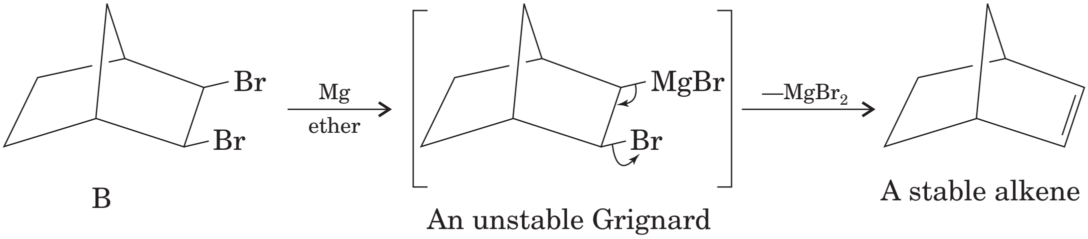
24. The dibromide A reacts with magnesium in dry ether to form a stable Grignard reagent, while the dibromide B does not. Explain.



Solution A 1,2-dibromide reacts with Mg to form an alkene plus $MgBr_2$. The Grignard reagent corresponding to the dibromide A does not undergo elimination of $MgBr_2$ to give an alkene because the alkene containing a double bond at the bridgehead position is too unstable to exist according to the Bredt's rule. A stable Grignard reagent is, therefore, obtained from A.



The Grignard reagent corresponding to the dibromide B, on the other hand, readily eliminates a molecule of $MgBr_2$ to form a stable alkene (the double bond is not at the bridgehead position). A Grignard reagent is, therefore, not obtained from B.



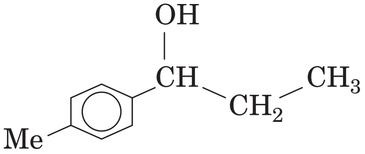
B

An unstable Grignard

A stable alkene

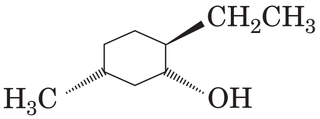
25. Identify the epoxides which react with CH_3CH_2MgBr to give the following alcohols after acidification:

(a)

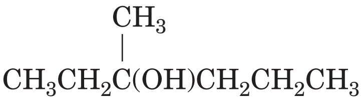


(b) $CH_3CH_2CH_2CH_2OH$

(c)



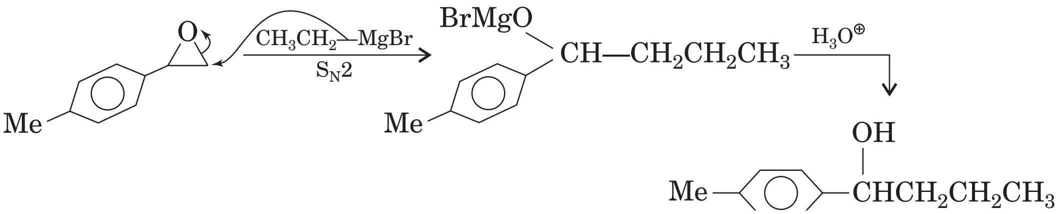
(d)



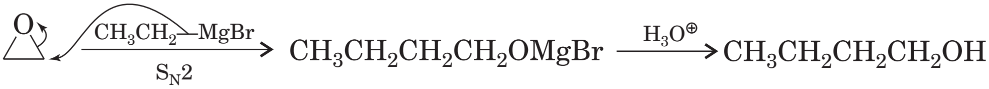
$CH_3CH_2C(CH_3)(OH)CH_2CH_2CH_3$

Solution

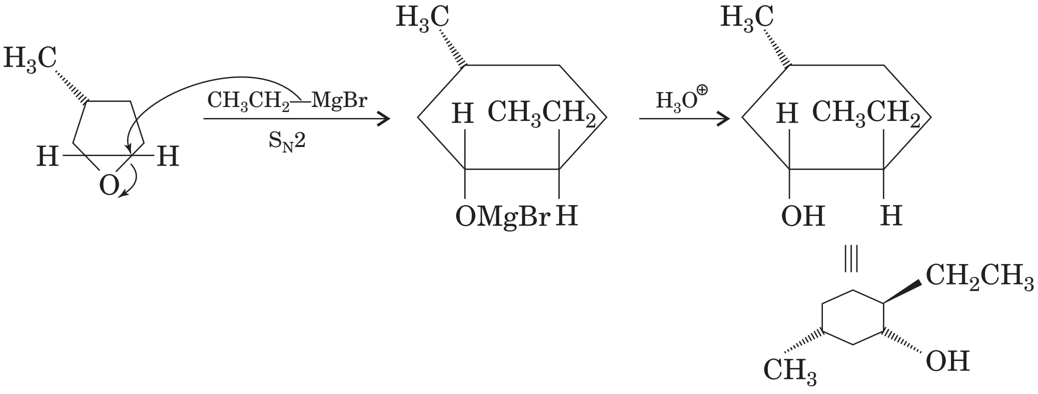
(a)



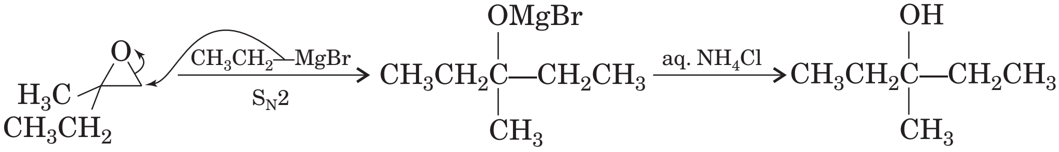
(b)



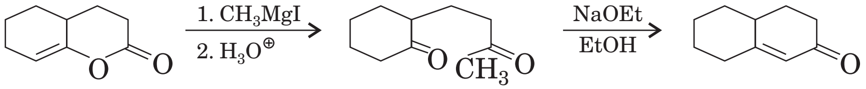
(c)



(d)

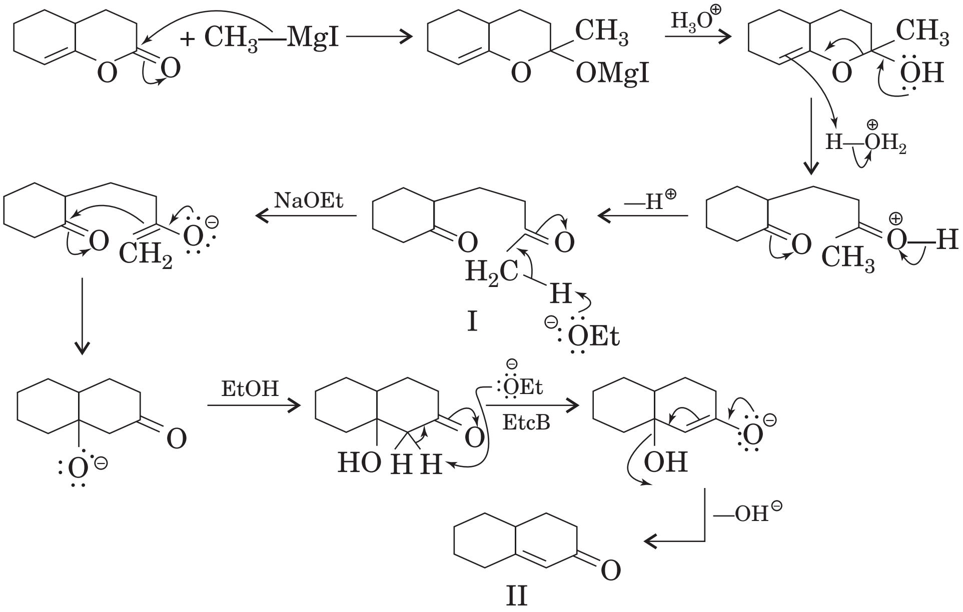


26. Offer a suitable mechanism for each step of the following transformation:



I II

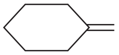
Solution The mechanism of this transformation may be given as follows:

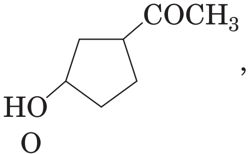


I is formed by a Grignard reaction followed by acid-catalysed ring opening and II is formed by an internal aldol.

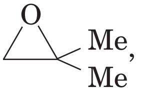
27. Predict the products expected to be formed when butyllithium ($CH_3CH_2CH_2CH_2Li$) is allowed to react with each of the following reagents:

(a) $CH_3CH_2C{\equiv}CH$, then 2-butanone and then aqueous NH_4Cl

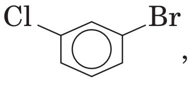
(b)  O, then aqueous NH_4Cl

(c) 

, then aqueous NH_4Cl

(d) 

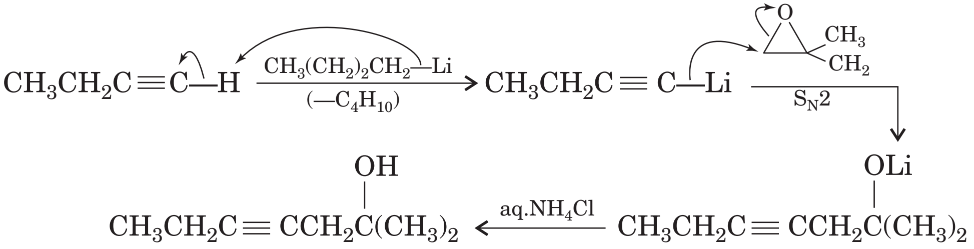
, then H_2O

(e) 

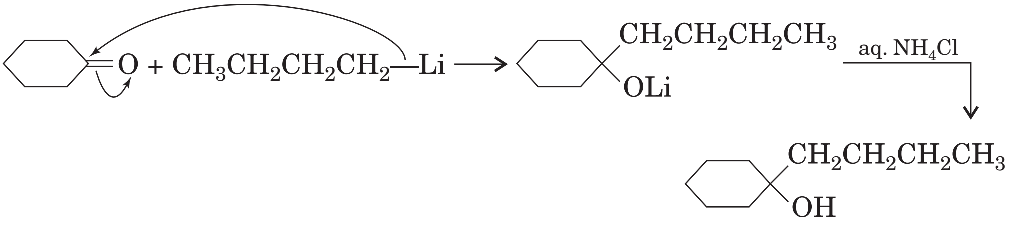
, then CO_2 and then $H_3O^{\oplus}$

Solution

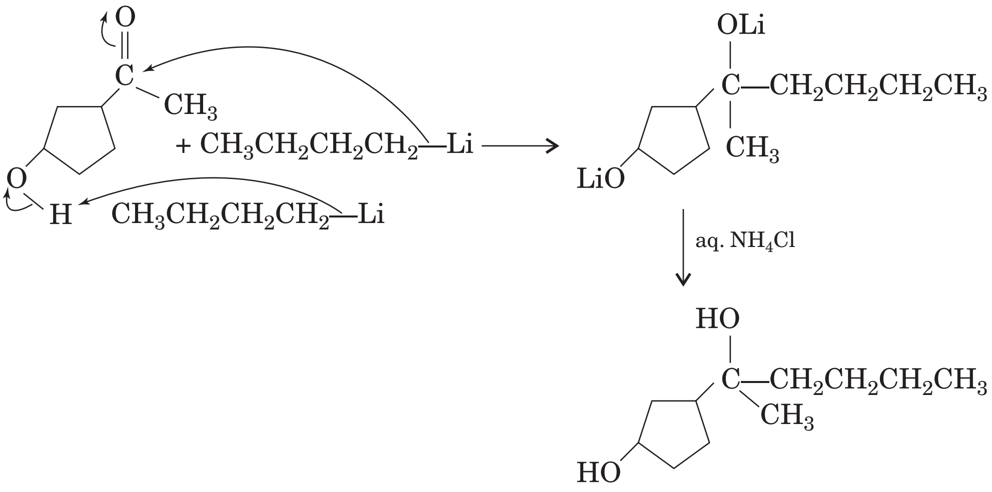
(a)



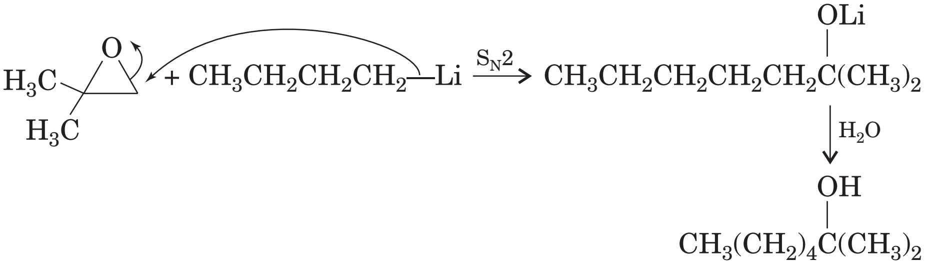
(b)



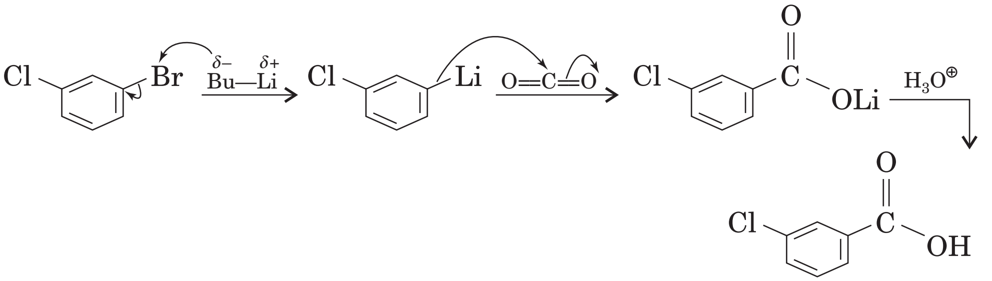
(c)



(d)

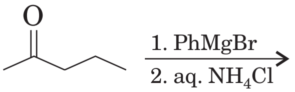


(e)

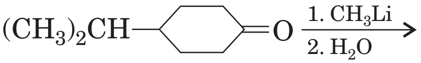


28. Draw all stereoisomers formed in each of the following reactions:

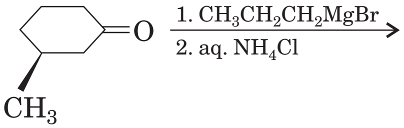
(a)



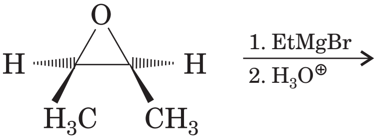
(b)



(c)

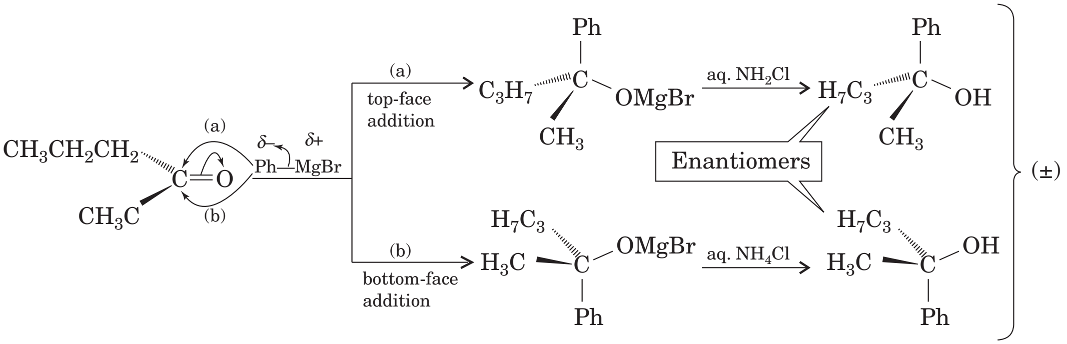


(d)

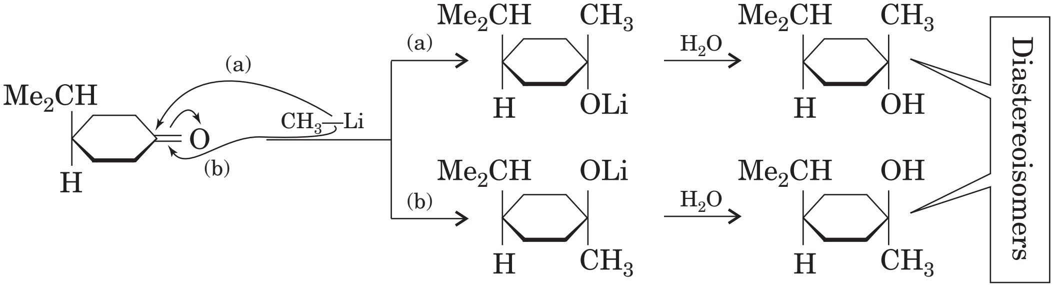


Solution

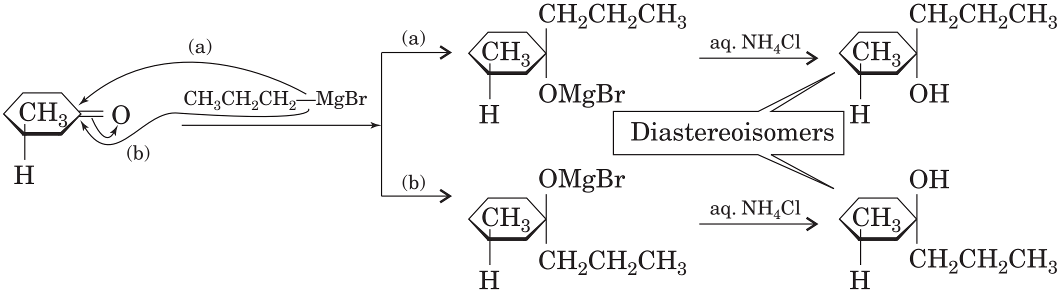
(a)



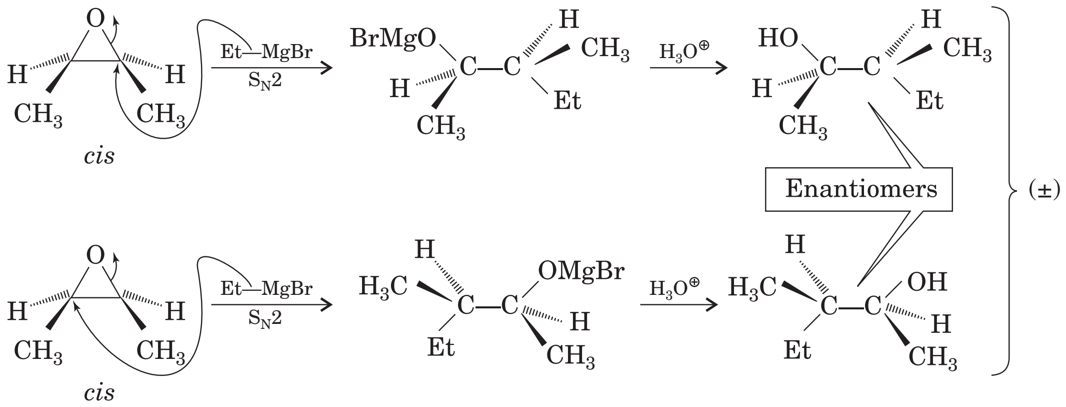
(b)



(c)

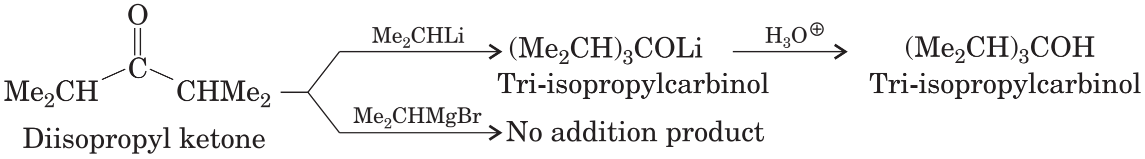


(d)

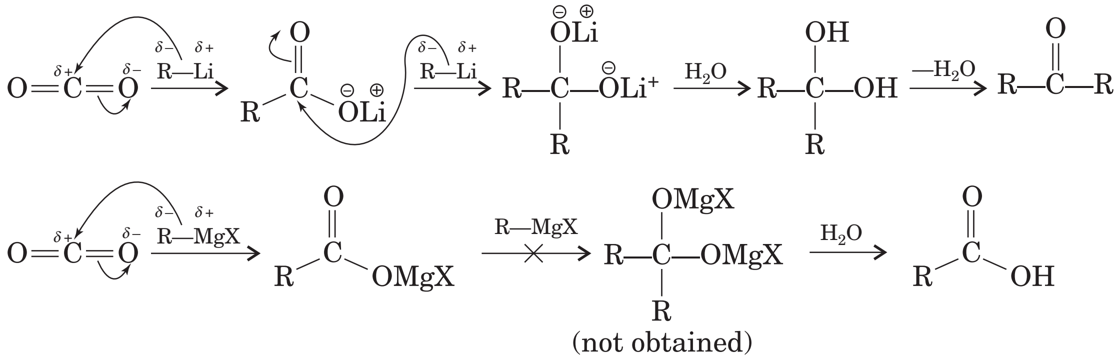


29. Why are organolithium compounds especially useful and often advantages over the organomagnesium compounds?

Solution Organolithium compounds are especially useful because they are more reactive reagents (C—Li bond is more polar than C—Mg bond) and can give normal addition products with sterically hindered ketones. The complicating side reactions like enolisation and reduction are also less important with organolithium compounds. For example, isopropyllithium adds to diisopropyl ketone (a hindered ketone) to give tri-isopropylcarbinol in good yield, whereas isopropylmagnesium bromide fails completely to give the normal addition product, i.e., the tertiary alcohol.

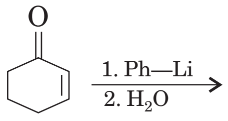


Unlike Grignard reagents two equivalent organolithium compounds reacts with CO$_2$ to give a ketone. Due to greater nucleophilicity of R—Li, compared to R—MgX, the former attack the carbonyl carbon of the intermediate carboxylate ion in which the carbonyl carbon possesses less positive character.

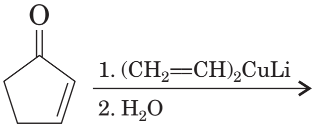


30. Draw the product expected to be obtained in each of the following reactions:

(a)

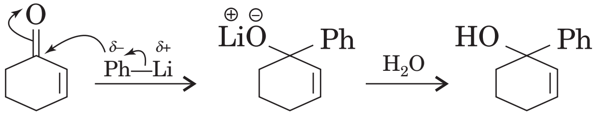


(b)

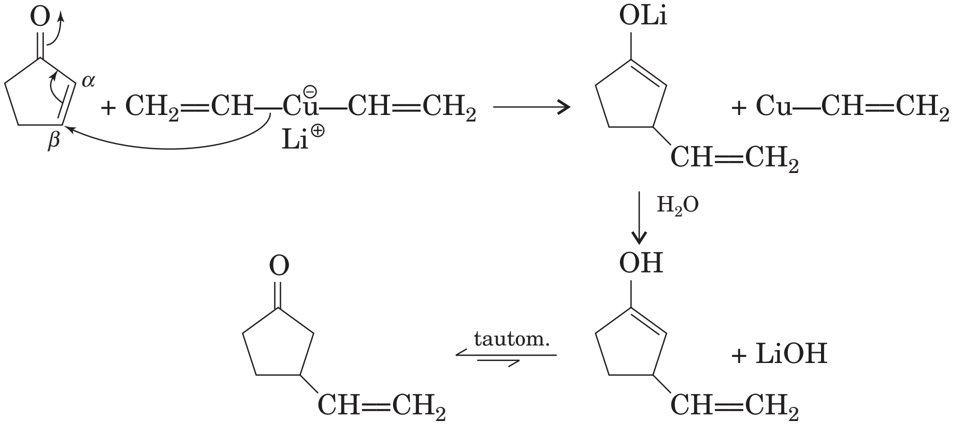


Solution

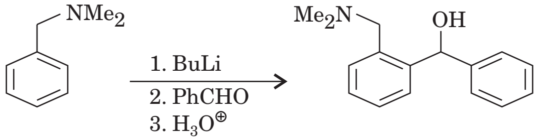
(a) Organolithium compounds react with α,β-unsaturated carbonyl compounds to give 1,2-addition products. Therefore, phenyl lithium reacts with 2-cyclohexanone as follows:



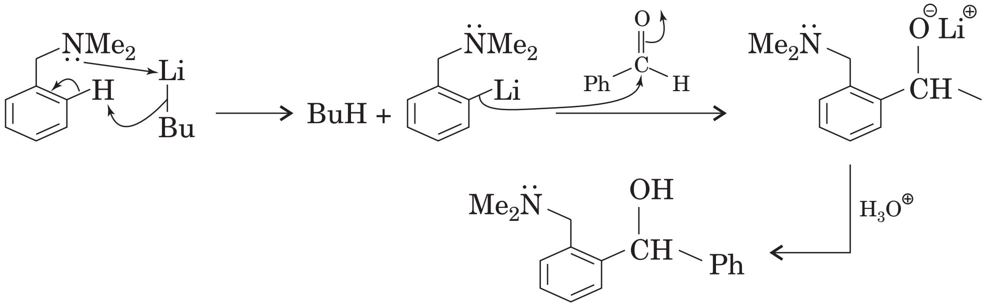
(b) Organocuprate reagents undergo 1,4-addition. The cuprate reagent adds a new vinyl group ($CH_2{=}CH{—}$) at the β-position of the α,β-unsaturated ketone.



31. Suggest a reasonable mechanism for the following reaction:

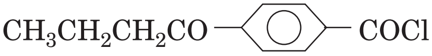


Solution The mechanism of the reaction involving *ortho*-lithiation followed by C—C bond formation takes place as follows:



32. Give the products of the reaction of Me_2CuLi (after hydrolysis) with the following compounds:

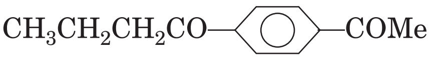
(a) $N{\equiv}C(CH_2)_6COCl$

(b)

$CH_3CH_2CH_2CO-C_6H_4-COCl$

(c) $EtO_2C(CH_2)_3COCl$

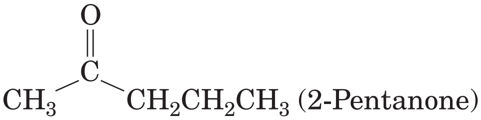
Solution

(a) $N{\equiv}C(CH_2)_6COMe$

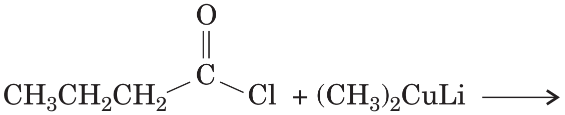
(b)

$CH_3CH_2CH_2CO-C_6H_4-COMe$

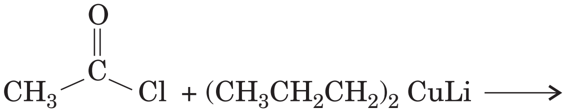
(c) $EtO_2C(CH_2)_3COMe$

33. Suggest two combinations of alcyl halide and cuprate reagent for the preparation of the following ketone:


$CH_3COCH_2CH_2CH_3$ (2-Pentanone)

Solution The two alkyl groups of the ketone are different. Therefore, one of them may come from the organocuprate and the other may come from the acid chloride. Hence, the two combinations are as follows:

(i)

$CH_3CH_2CH_2COCl + (CH_3)_2CuLi \longrightarrow$

(ii)

$CH_3COCl + (CH_3CH_2CH_2)_2CuLi \longrightarrow$

34. Suggest two possible methods for the Corey–Posner, Whitesids–House synthesis of 2-methylpropane and indicate which one is much better. Give your reasoning.

Solution

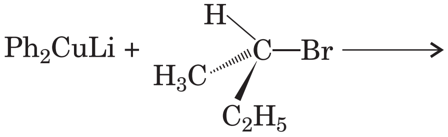
The two possible methods for the synthesis of 2-methylpropane are as follows:

Method 1: $CH_3I \xrightarrow[-LiI]{2Li} \underset{(2\ \text{equiv.})}{CH_3Li} \xrightarrow[-LiI]{CuI} (CH_3)_2CuLi \xrightarrow[\substack{-LiBr\\-CuCH_3}]{(CH_3)_2CHBr} (CH_3)_2CHCH_3$

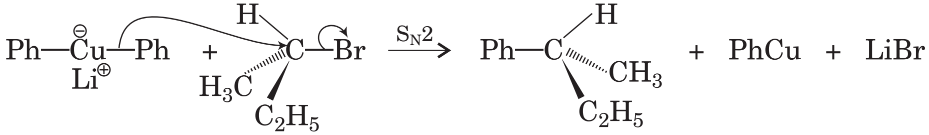
Method 2: $(CH_3)_2CHBr \xrightarrow[-LiBr]{2Li} \underset{(2\ \text{equiv.})}{(CH_3)_2CHLi} \xrightarrow[-LiI]{CuI} [(CH_3)_2CH]_2CuLi \xrightarrow[\substack{-LiI\\-(CH_3)_2CHCu}]{CH_3I} [(CH_3)_2CHCH_3$

The final step of this synthetic process is an S_N2 reaction which is much susceptible to steric hindrance. Since CH_3I is a much better S_N2 substrate than $(CH_3)_2$ CHBr from steric point of view, the method 2 is much better than the method 1.

35. Predict the product of the following reaction and mention its configuration (*R* or *S*):

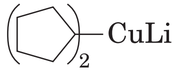


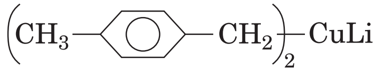
Solution The reaction of lithium diphenylcuprate with this optically active bromide yields 2-phenylbutane with high net inversion of configuration (S_N2). Therefore, the product is (*R*)-2-phenylbutane.



(*S*)-2-Bromobutane (*R*)-2-Phenylbutane

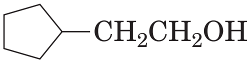
36. What alcohols would be produced from the reaction of ethylene oxide with the following organocuprates followed by addition of dilute acid?

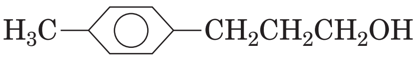
(a) 

(b) 

(c) $(CH_3CH_2CH_2)_2CuLi$

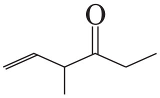
Solution

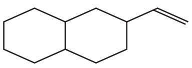
(a) 

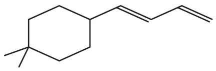
(b) 

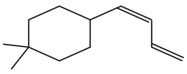
(c) $CH_3(CH_2)_4OH$

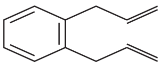
37. Give the reaction of $(CH_2{=}CH)_2CuLi$ with an alkyl bromide to produce each of the following compounds:

(a) 

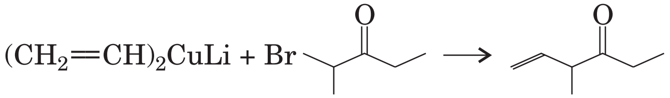
(b) 

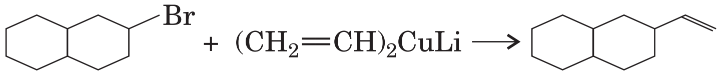
(c) 

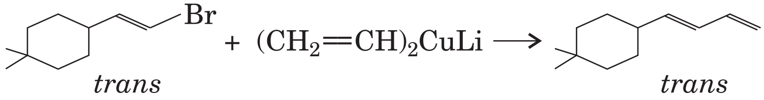
(d) 

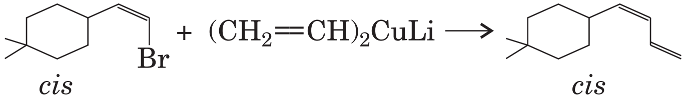
(e) 

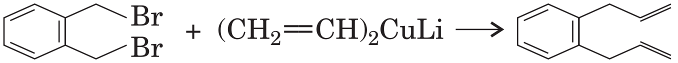
Solution

(a) 

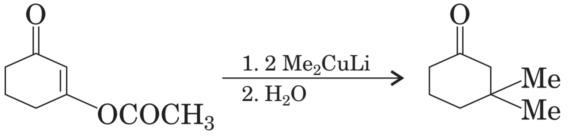
(b) 

(c) 

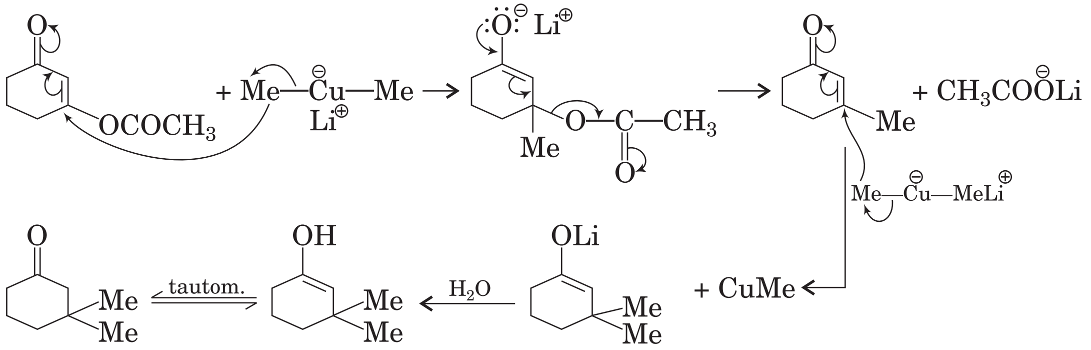
(d) 

(e) 

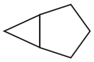
38. Give a curved-arrow mechanism for the following reaction:

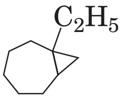


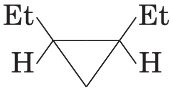
Solution



39. **Provide retrosynthetic analysis and synthesis for each of the following cyclopropane derivatives using the Simmons–Smith reagent (iodomethylzinc iodide):**

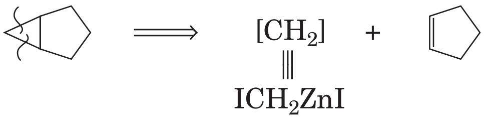
(a) 

(b) 

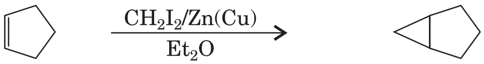
(c) 

Solution

(a) **Retrosynthetic analysis** In cyclopropane synthesis using the Simmons–Smith reagent, a CH_2 unit is transferred to a double bond. Therefore, retrosynthetically we have to disconnect the bonds to a CH_2 group of a three-membered ring to identify the starting alkene.

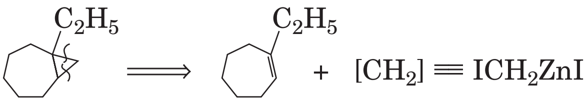


Synthesis

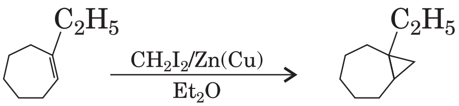


Bicyclo[3.1.0]hexane

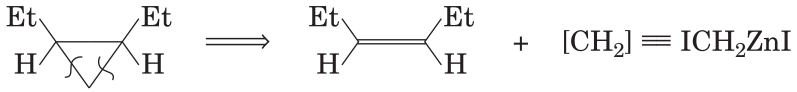
(b) **Retrosynthetic analysis**



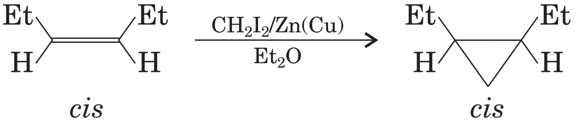
Synthesis



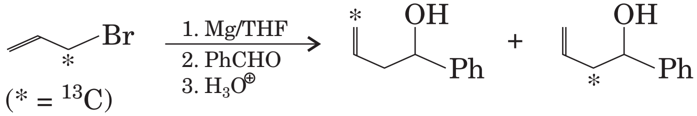
(c) **Retrosynthetic analysis**



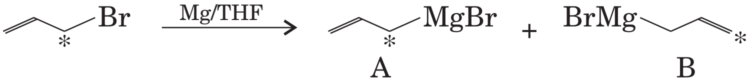
Synthesis



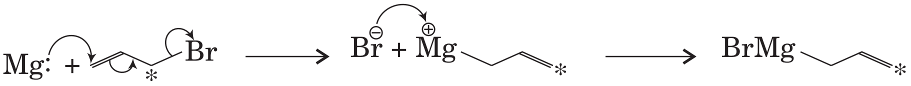
40. Account for the formation of the products (differs in isotopic label) in the following reaction:

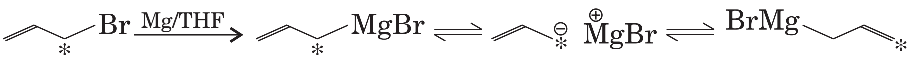


Solution The reaction may be mechanically interpreted as follows:

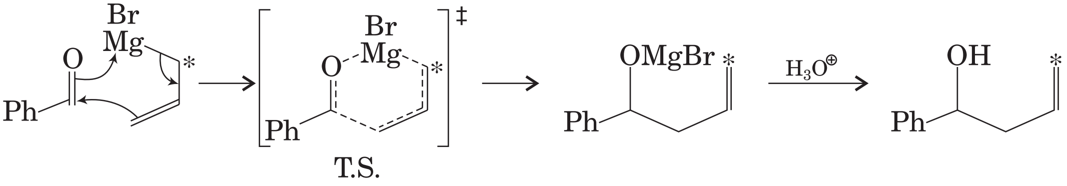


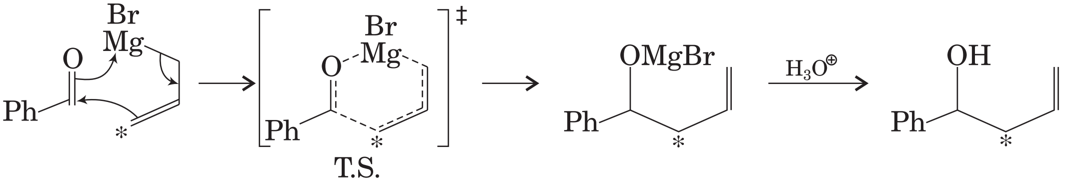
The allylic Grignard reagent B can be obtained by attack of the metal at the other end of the allylic system, or after formation by equilibrium with the allyl anion.





The two allylic Grignard reagents would have equal energies and would be formed in equal amounts. These two then react with benzaldehyde following a cyclic mechanism to give the products.





STUDY PROBLEMS

1. Explain why Grignard reagents in ethereal solution exists as dietherate.

2. Arrange the following carbon–metal bonds in order of increasing polarity:

C—Cu, C—Mg, C—Zn, C—Li, C—Pb, C—Cd

3. How would you distinguish primary, secondary and tertiary amines with the help of Zerewitinoff procedure?

4. The R group in an alkyl halide bears a partial positive charge ($\overset{\delta+}{R} - \overset{\delta-}{X}$, X = Cl, Br, I). Convert it into a compound in which the same R group carries partial negative charge (a case of *umpolung*).

5. How can an alkyl halide be converted (reduced) to a hydrocarbon without using the usual reducing agents?

[**Hint:** $R—X + Mg \xrightarrow{\text{ether}} RMgX \xrightarrow{H_3O^{\oplus}} RH$]

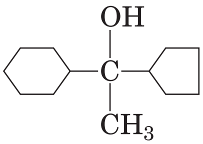
6. Write structures of the isomeric alkylmagnesium bromides which on hydrolysis produce 2-methylbutane.

7. Complete the following reaction sequence and comment ($\overset{*}{C} = {}^{14}C$):

$$RMgBr + \overset{*}{C}O_2 \longrightarrow ? \xrightarrow{H_3O^{\oplus}} ? \xrightarrow[2.\ CH_2N_2]{1.\ SOCl_2} ? \xrightarrow{Ag_2O} ? \xrightarrow{H_2O} ?$$

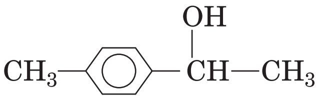
8. Provide retrosynthetic analysis and synthesis for each of the following alcohols, starting with appropriate alkyl or aryl halides:

(a)



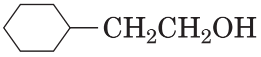
(three ways)

(b)



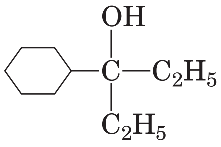
(two ways)

(c)



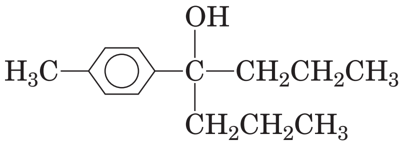
(two ways)

(d)



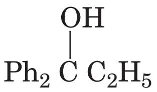
(three ways)

(e)



(three ways)

(f)



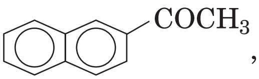
$Ph_2\overset{OH}{C}C_2H_5$

(three ways)

9. What products would you expect from the reaction of ethylmagnesium bromide with each of the following compounds?

(a) $CH_3C{\equiv}CH$, then CH_3CHO, then $H_3O^{\oplus}$

(b) $PhCO_2Me$, then aqueous NH_4Cl

(c) 

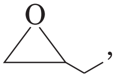
, then aqueous NH_4Cl

(d) D_2O

(e) H_2O

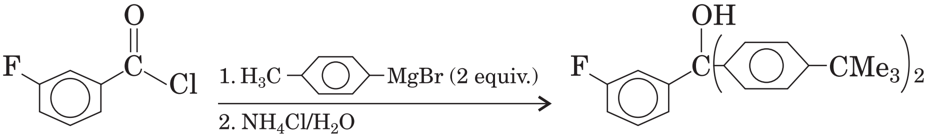
(f) $HC{\equiv}CH$, then CO_2 (2 equiv.), then $H_3O^{\oplus}$

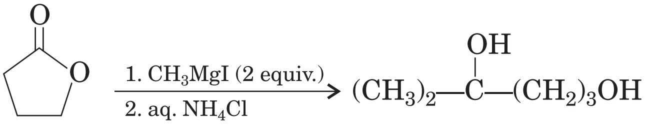
(g) SO_2, then $H_3O^{\oplus}$

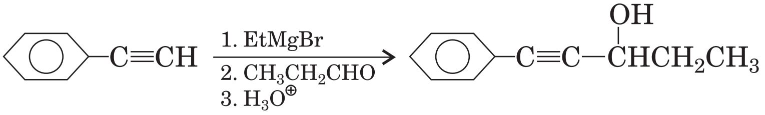
(h) 

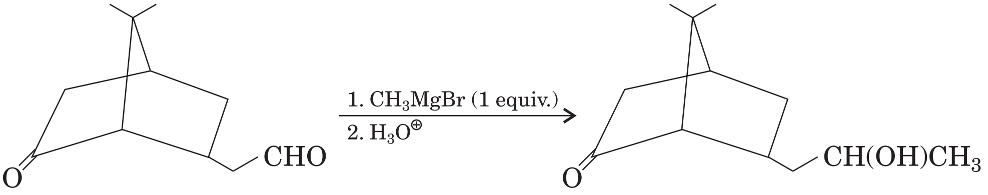
, then $H_3O^{\oplus}$

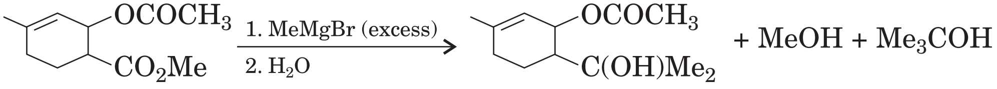
10. Provide a reasonable mechanism for each of the following reactions:

(a) 

(b) 

(c) 

(d) 

(e) 

11. Give the structures of A–D in the following reaction sequence:

$$\text{EtMeCHCOPh} \xrightarrow[\text{2. aq. }NH_4Cl]{\text{1. PhMgBr}} A \xrightarrow{H^{\oplus}} B \xrightarrow[\text{2. Zn/}H_2O]{\text{1. }O_3} C + D$$

12. Which one of the following two methods is appropriate for the synthesis of 2,2-dimethylpropanoic acid (Me_3CCOOH) and why?

(a) $(CH_3)_3CCl \xrightarrow[\text{ether}]{\text{Mg}} (CH_3)_3CMgCl \xrightarrow[\text{2. }H_3O^{\oplus}]{\text{1. }CO_2} (CH_3)_3CCOOH$

(b) $(CH_3)_3CCl \xrightarrow{\text{KCN}} (CH_3)_3C{-}CN \xrightarrow{H_3O^{\oplus}/\Delta} (CH_3)_3C{-}COOH$

13. How would you prepare $Me_3C{-}NH_2$ by using a Grignard reaction?

14. When $PhCH_2Br$ is allowed to react with metallic magnesium in dry ether medium, a hydrocarbon $A(C_{14}H_{14})$ is obtained along with $PhCH_2MgBr$. Identify A and explain its formation.

15. Explain the following observations:

(a) Grignard reagent may act as a reducing agent.

(b) Alkyl fluorides do not react with magnesium to form Grignard reagents.

(c) Ethylene oxide undergoes cleavage by RMgX, but Et_2O or THF does not.

(d) Acetone reacts with EtMgBr to form an achiral 3° alcohol, whereas 2-pentanone reacts with EMgBr to form a chiral 3° alcohol.

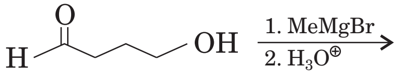
(e) A Grignard reagent cannot be prepared from a compound containing an —OH group.

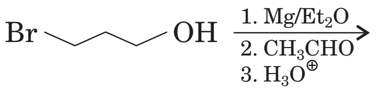
(f) A keto group of a haloketone must be protected before preparing a Grignard reagent using it.

(g) Grignard reagents act as strong bases.

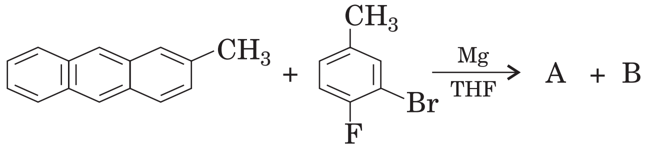
[**Hint:** Since alkanes (R—H) are very weak acids (p*K*a = 55–60), their conjugate bases, i.e., the carbanions ($\overset{\ominus}{R}{:}$) are very strong bases. For this reason, Grignard reagents that can provide $\overset{\ominus}{R}{:}\,(\overset{\delta-}{R}—\overset{\delta+}{Mg}X)$ are strong bases.]

(h) Neither of the following two methods of making pentan-1,4-diol will work:

(i)


(ii)


16. (a) Predict the products of the following reaction and comment on their optical activity:



(b) In the preparation of ethynylmagnesium bromide (HC≡CMgBr) by the transmetallation reaction involving acetylene (HC≡CH) and ethylmagnesium bromide (CH_3CH_2MgBr), ethylmagnesium bromide is added to a large excess of acetylene in THF solution. The two side reactions that can take place are as follows:

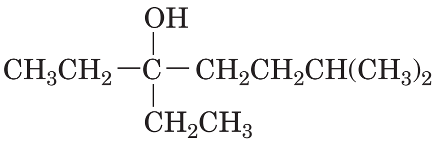
(i) $HC{\equiv}CMgBr + CH_3CH_2MgBr \rightarrow CH_3CH_3 + BrMgC{\equiv}CMgBr$

(ii) $2HC{\equiv}CMgBr \rightleftharpoons H{-}C{\equiv}C{-}H + BrMgC{\equiv}CMgBr$

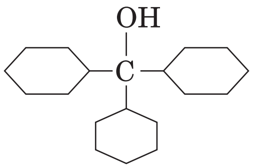
Suggest a mechanism for each of the above two reactions and explain why an excess of acetylene is important for avoiding these reactions. Tetrahydrofuran (THF) is used as a solvent in this reaction because the undesired by-product BrMgC≡CMgBr is relatively soluble in it. Explain why it is important for this by-product to be soluble in the solvent to suppress these side reactions.

[**Hint:** (a) Formation of an aryne followed by a Diels–Alder reaction with anthracene derivative.]

17. What ester and Grignard reagent are required to synthesize each of the following alcohols?

(a) 

$$CH_3CH_2-\underset{CH_2CH_3}{\overset{OH}{C}}-CH_2CH_2CH(CH_3)_2$$

(b) 

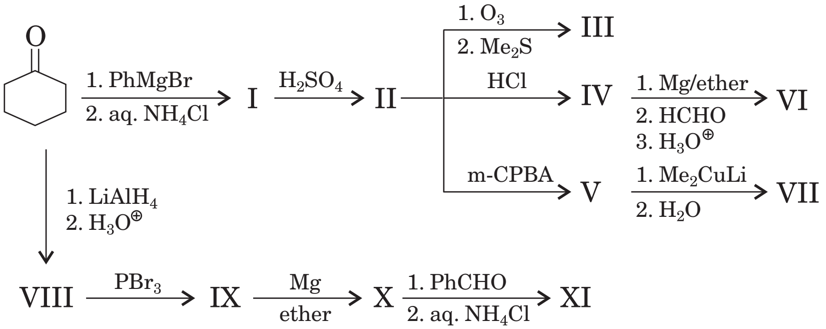
(c) $PhCHOH\,(CH_2CH_2CH_2CH_3)_2$

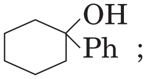
18. (a) Propose at least three methods to convert $PhCH_2CH_2Br$ to $PhCH_2CH_3$.

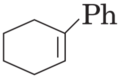
[**Hint:** (i) $PhCH_2CH_2Br \xrightarrow[\text{2. H}_2\text{O}]{\text{1. Mg/ether}} PhCH_2CH_3$; (ii) $PhCH_2CH_2Br \xrightarrow[\text{2. H}_3\text{O}^{\oplus}]{\text{1. LiAlH}_4} PhCH_2CH_3$; (iii) $PhCH_2CH_2Br \xrightarrow[\Delta]{\text{alc. KOH}} PhCH{=}CH_2 \xrightarrow{H_2/Pt} PhCH_2CH_3$]

(b) Synthesize 1-methylcyclohexene from cyclohexanone and methanol using a Grignard reaction in one of the steps.

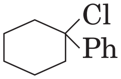
19. Identify the compounds I–XI in the following reaction sequence and indicate which of them are isomeric:

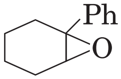


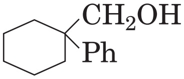
[**Hint:** I ⇒ 

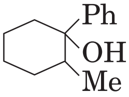
; II ⇒ 

; III ⇒ $PhCO(CH_2)_4CHO$;

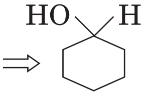
IV ⇒ 

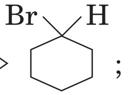
; V ⇒ 

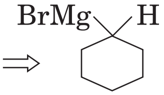
; VI ⇒ 

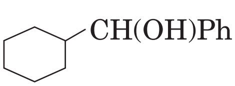
; VII ⇒ 

;

VIII ⇒ 

; IX ⇒ 

; X ⇒ 

; XI ⇒ 

]

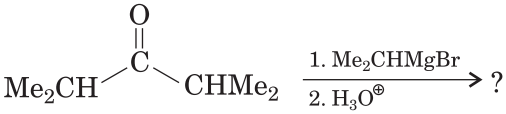
20. Complete the following equations and comment where necessary:

(a) $\underset{\text{(3 equiv.)}}{PhMgBr} + (EtO)_2CO \xrightarrow[\text{2. H}_3\text{O}^{\oplus}]{\text{1. Et}_2\text{O}} ?$

(b) $Me_2C{=}C{=}O + EtMgBr \xrightarrow[\text{2. H}_3\text{O}^{\oplus}]{\text{1. Et}_2\text{O}} ?$

(c) $n\text{-}PrMgBr + MeC(OMe)_3 \xrightarrow[\text{2. H}_3\text{O}^{\oplus}]{\text{1. Et}_2\text{O}} ?$

(d) $C_6H_{11}MgBr + BrCH_2CBr{=}CH_2 \xrightarrow{Et_2O} ?$

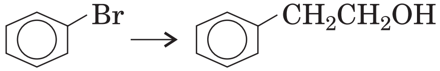
(e) 

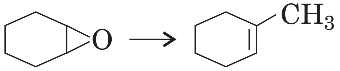
$$Me_2CH-\overset{\overset{O}{||}}{C}-CHMe_2 \xrightarrow[2.\ H_3O^{\oplus}]{1.\ Me_2CHMgBr} ?$$

[**Hint:** (d) Only the allylic bromine is sufficiently reactive to undergo displacement]

21. When $Br(CH_2)_4OD$ is treated with magnesium in dry ether and the resultant compound is hydrolysed, 1-butanol ($CH_3CH_2CH_2CH_2OH$) is obtained. Explain this observation.

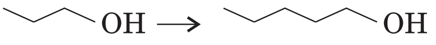
22. How would you carry out the following transformations?

(a) 

(b) 

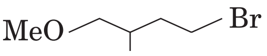
(c) $Me_2CHCH_2OH \longrightarrow Me_2CHCH_2CH_2CH(OH)CH_3$

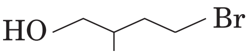
(d) $CH_3CH_2CH_2C{\equiv}CH \longrightarrow CH_3CH_2CH_2\ C{\equiv}C\ CH_2CH_2OH$

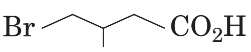
(e) 

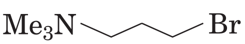
(f) $PhCl \longrightarrow PhCOOH$

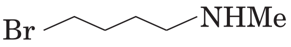
23. Which of the following alkyl halides could be used successfully to prepare a Grignard reagent?

(a) 

(b) 

(c) 

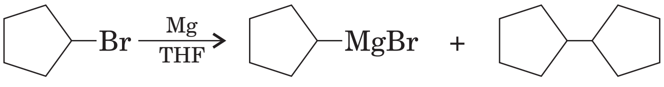
(d) 

(e) 

24. A dibromide loses one bromine atom when treated with aqueous sodium hydroxide. When the dibromide is allowed to react with metallic magnesium in dry ether and the resulting compound is treated with dilute acid, toluene ($Ph{-}CH_3$) is obtained. Predict the possible structures of the dibromide and give your reasoning.

[**Hint:** The dibromide may be *o*-$BrC_6H_4CH_2Br$, *m*-$BrC_6H_4CH_2Br$ or *p*-$BrC_6H_4CH_2Br$.]

25. Dimerisation is a side reaction that takes place during the preparation of a Grignard reagent. Suggest a mechanism that accounts for the formation of the dimer in the following reaction.



(adimer)

26. (a) What generalisation can be made as to the nature of the C—M bond and the electronegativity of the metal? (b) What kind of bond is expected to be formed between carbon and (i) an alkali metal (e.g., Na, K, etc.) and (ii) a group 2 metal? Give examples. (c) Give an example of a compound containing C—M bond which has little or no ionic character.

[**Hint:** (b) (i) ionic ($C_2\overset{\ominus}{H_5}K^{\oplus}$), (ii) highly polar covalent ($\overset{\delta-}{CH_3}{-}\overset{\delta+}{Mg}I$), (c) covalent ($Me_2Hg$).]

27. What is the main difference between organolithium compounds and Grignard reagents?

[**Hint:** The main difference between the two reagents is that lithium compounds add to an ethylenic bond whereas Grignard reagents do not. For example, $BuLi + CH_2{=}CH_2 \longrightarrow BuCH_2CH_2Li$.]

28. Identify the compounds A—E in the following reaction sequence:

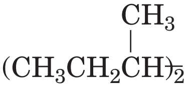
$$CH_3COCH_3 \xrightarrow{NaNH_2} A \xrightarrow{C_2H_2} B \xrightarrow{H_3O^{\oplus}} C \xrightarrow[Pd]{H_2\,(1\,mol)} D \xrightarrow[400°C]{Al_2O_3} E$$

29. What organocuprate reagent is needed to convert $CH_3CH_2CH_2COCl$ to each ketone?

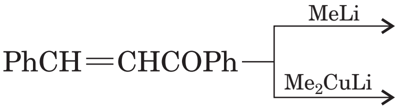
(a) $CH_3CH_2CH_2COCH_3$

(b) $CH_3CH_2CH_2CO\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2CH_3$

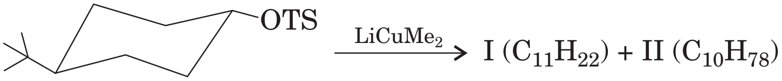
(c) $CH_3CH_2CH_2COPh$

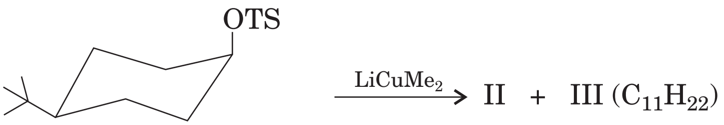
[**Hint:** (a) $(CH_3)_2CuLi$ (b)  $(CH_3CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}H)_2\,CuLi$ (c) Ph_2CuLi]

30. Give the products of the following reactions and explain:



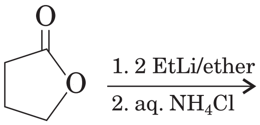
31. Predict reasonable structures for compounds I, II and III in the following reactions:

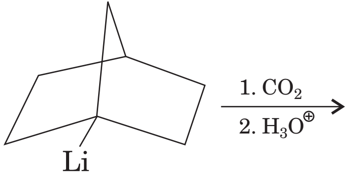


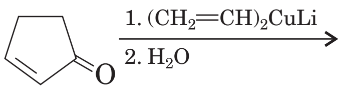


The compound III is relatively more stable than the compound I.

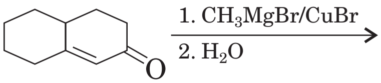
32. Predict the product expected to be formed in each of the following reactions:

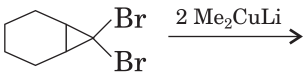
(a) 

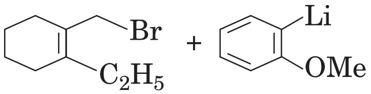
(b) 

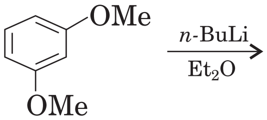
(c) 

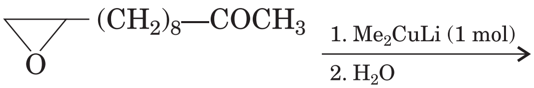
(d) $Me_2C{=}C(CO_2Et_2) \xrightarrow[2.\ H_2O]{1.\ CH_3MgI/CuCl}$

(e) 

(f) 

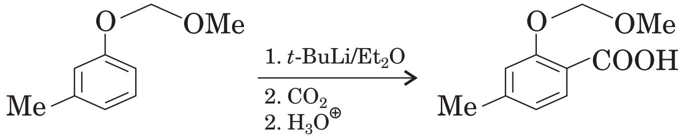
(g) 

(h) 

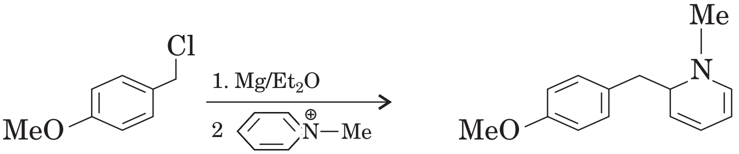
(i) 

33. (a) Provide a reasonable mechanism for each of the following reactions:

(i)



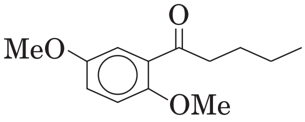
(ii)



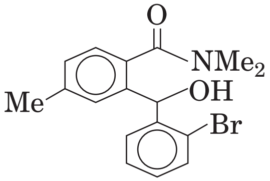
(b) Pyridine reacts with PhLi to give 2-phenylpyridine and LiH in a reaction analogous to the reaction of pyridine with $NaNH_2$. Suggest a mechanism for the reaction.

34. How would you prepare the following compounds using ortholithiation procedure?

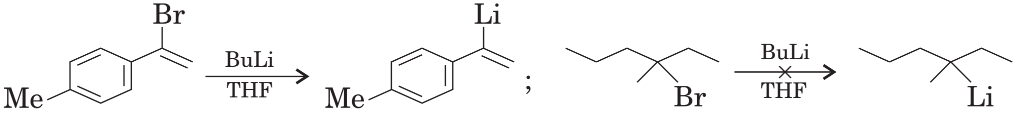
(a)



(b)



35. Explain why it is possible to make the organolithium compound A, but not the organolithium compound B in the following reactions:

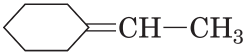


A B

[**Hint:** Vinyl (sp^2) carbanions are more stable than saturated (sp^3) carbanions because of the greater *s* character in the C—Li a bond, and for this reason, the first reaction occurs. On the other hand, the *t*-alkylcarbanion is less stable than a primary alkyl carbanion (e.g., BuLi). So, the second reaction does not take place.]

36. Give the structure of the product expected to be formed when each of the following compounds is allowed to react with CH_2I_2 in the presence of Zn(Cu):

(a)



(b) (*E*)-3-methyl-2-pentene

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1. Posner, G. H., *An introduction to synthesis using organo-copper reagents*; Wiley: New York, 1980.
2. Millen, R. B. and McGravey, G. *J. Org. Chem.*, 1979, *44*, 4623.
3. Paul, R. J. *Organometallic Reagents in Synthesis*; Oxford University Press.
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3

The Logic of Organic Synthesis

Chapter Outline

Introduction

3.1 Retrosynthetic Analysis
- 3.1.1 A Few Terms Related to Retrosynthesis
- 3.1.2 Guidelines for Choosing Suitable Disconnections
- 3.1.3 Guidelines for the Order of Events in the Synthesis of Aromatic Compounds
- 3.1.4 One-Group C–X Disconnections
- 3.1.5 Two-Group C—X Disconnections
- 3.1.6 One-group C—C Disconnections
- 3.1.7 The Problem of Regioselectivity and its Solution in Alkylation of Ketone and in Michael Addition
- 3.1.8 Synthesis of Alkenes
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- 3.2.2 Synthesis of Three-, Four-, Five- and Six-Membered Saturated Heterocycles
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- 3.2.4 Syntheis of Large Rings: Application of High Dilution Technique

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- 3.3.1 Stereoselective and Stereospecific Reactions
- 3.3.2 Asymmetric Synthesis

INTRODUCTION

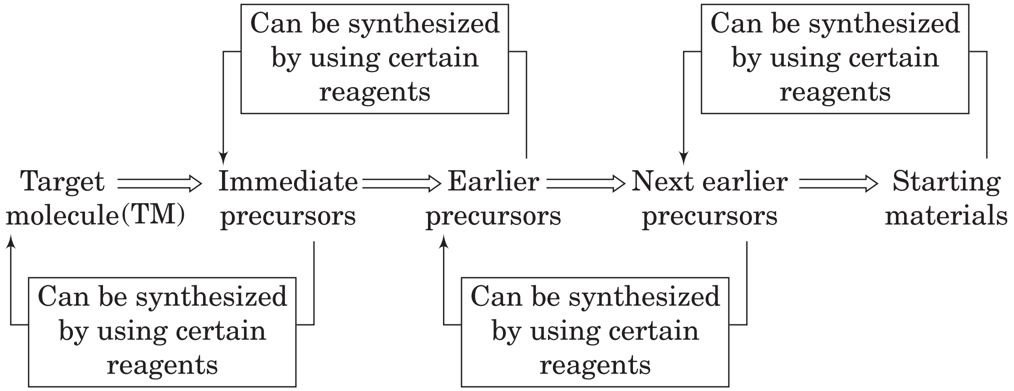
The ideal synthesis of an organic compound involves conversion of the readily available and relatively cheap starting materials, which are the most logical precursor in a given sequence of reactions, into the pure target molecule (TM) by the least number of steps and in the highest possible yield. Synthesis is one of the major areas of organic chemistry. A synthesis may be a simple one-step reaction, or it may involve many steps and incorporate a subtle strategy for assembling the correct carbon skeleton with all the functional groups in the right positions. Organic chemists use synthesis for a variety of purposes. Syntheses have been used as the final proof molecular structure for natural products isolated from plant and animal sources. In more practical terms, synthesis can provide a supply of important compounds used as medicines, insecticides, fertilizers, polymers, etc. Synthesis can also be used to prepare compounds previously unknown but predicted to be useful. The chemical instruments required during organic synthesis are as follows:

1. Methods of C—C bond formation
2. Methods of C—N and C—O bond formations
3. Protection and deprotection of functional groups/position
4. Activation and deactivation of functional groups/position
5. Ring-opening and ring-closure
6. Ring-expansion and ring-contraction
7. Dehydrating and condensing agents
8. Functional group removal

In solving multistep synthesis problems, we will rarely be able to 'see' the solution immediately. These problems are best tackled systematically, working backward and considering alternative routes. This backward approach to synthesis is known as *retrosynthetic analysis*. This important topic along with two other topics like *strategy of ring synthesis* and *asymmetric synthesis* have been discussed in this chapter.

3.1 RETROSYNTHETIC ANALYSIS

From the middle of nineteenth century, synthetic methodologies were developed by 'associative mental processes', i.e., thinking of analogy. But when atomic structure is better understood, and the mechanism of bond-making and bond-breaking possesses become progressively more clear, organic syntheses become more planned. This is reflected in some landmark syntheses of a number of molecules like camphor (by Komppa in 1903), α-terpineol (by Perkin in 1904), atropine (by Robinson in 1917), Quinine (by Woodward in 1944), etc. After the middle of twentieth century, synthetic organic chemistry showed a notable growth due to the following reasons: (i) organic reaction mechanism, stereochemistry, and conformation of the molecules are better understood; (ii) spectroscopic methods are developed for identification of organic molecules; (iii) chromatographic techniques are developed for purifying organic compounds, and (iv) a number of chemoselective, regioselective, and stereoselective reagents and catalysts are developed. But even all of these developments, synthetic process remain target oriented and chemists are guided by the structure of the TM alone. Chemists used to select the right starting material, mostly by trial and error method. If one starting material is failed, then another one is tried. This selection of the starting material is actually the key to the success of synthesis of molecules having quite complex structures like strychnine, morphin, cedrol, reserpine, etc. Since 1970, a new idea came in the field of organic synthesis mainly due to the efforts of Professor E.J. Corey of Harward University, who is honoured with the Nobel Prize 1990 in Chemistry and this approach is known as 'retrosynthesis' (*retro*, Latin, backward). The sequence of transformation that would lead to the desired product(TM) is often too complex to predict a path from beginning to the end. In that case, since we know where we want to finish (the TM) but not from where to start, we envisage the sequence of steps that is required in a backward fashion, one step at a time. At first, we identify the immediate precursors that would react to give the TM. These precursors in turn become new intermediate TMs and we identify the next set of precursors that would react to form them, and so on. This process is repeated until we have worked backward to compounds which are so simple that they are either easily available commercially or can be easily synthesized in the laboratory.


Can be synthesized by using certain reagents
Can be synthesized by using certain reagents
Target molecule(TM)
Immediate precursors
Earlier precursors
Next earlier precursors
Starting materials
Can be synthesized by using certain reagents
Can be synthesized by using certain reagents

Once the retrosynthetic analysis is completed and the simplest starting materials are identified, a synthesis of the target molecule is planned in the forward direction. This backward approach to synthesis is called *retrosynthetic analysis*. Since in this approach a strategic bond in the molecule is broken or disconnected (by mental processes) to give the starting materials, it is also called *synthesis by disconnection approach*. If more than one route work well, it is necessary to try several approaches in the laboratory in order to find out the most efficient or successful route.

3.1.1 A Few Terms Related to Retrosynthesis

3.1.1.1 Target Molecule

The molecule to be synthesized, i.e. the molecule whose synthesis is being planned is called the target molecule (TM).

3.1.1.2 Retrosynthetic Arrow

An open-ended or hollow arrow '⇒', used to indicate the reverse of a synthetic reaction, i.e., to signify a backward (retro) step is called a retrosynthetic arrow.

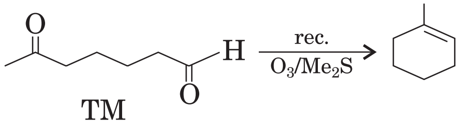
[It is used as a symbol for disconnection, FGI, FGA, etc., and usually the bond going to be cleaved, FGI, FGA, etc., are written over it.]

3.1.1.3 Disconnection

Disconnection is an imaginary bond cleavage, corresponding to the reverse of a real and workable reaction. This cleavage of a bond leads to the formation of two ionic fragments of which one is positively charged and the other is negatively charged. Therefore, disconnection is an analytical operation which breaks a bond mentally and converts a target molecule into two charged fragment from which we may get the actual reagents required for the synthesis. [It is helpful to indicate the side of disconnection with a wiggly line.]

3.1.1.4 Reconnection

During retrosynthetic analysis, it is the joining up of a bond in the target molecule that will be broken during the forward synthesis and this operation is called *reconnection*. For example



3.1.1.5 Synthon

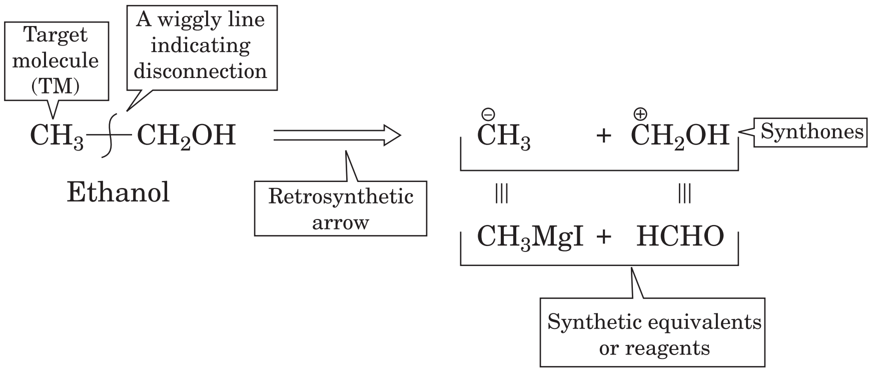
A *synthon* is an idealized fragment, usually a cation or an anion (real or imaginary), generated as a result of disconnection of a strategic bond in a molecule. It may or may not be an intermediate in the corresponding reaction. Synthones need to be replaced by reagents or synthetic equivalents in a suggested synthesis. [The functional group containing portion of the TM is called *retron*.]

3.1.1.6 Synthetic Equivalent or Reagent

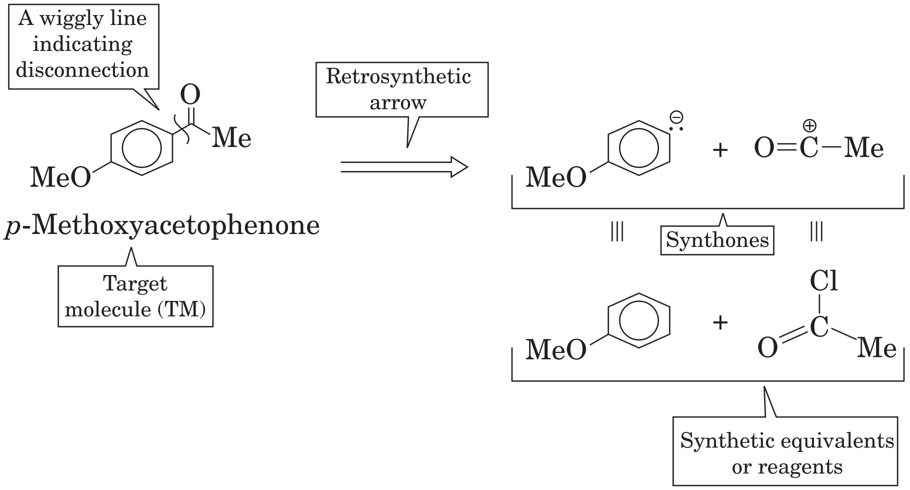
A real chemical compound used as the equivalent of a synthon is called a *synthetic equivalent (SE)* or a *reagent*.

The aforesaid terms can be well illustrated by the following examples:

(i)



(ii)



A wiggly line indicating disconnection

p-Methoxyacetophenone

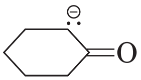
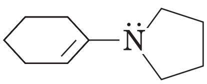
Target molecule (TM)

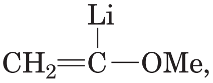
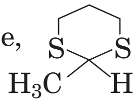
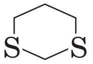
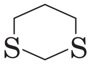
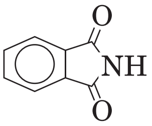
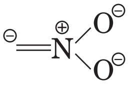
Retrosynthetic arrow

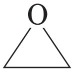
Synthones

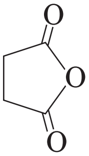
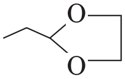
Synthetic equivalents or reagents

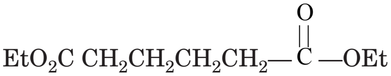
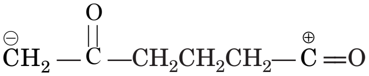
Table 3.1 Some common nucleophilic and electrophilic synthons and their synthetic equivalents

	Synthons	Synthetic Equivalents
(a) Nucleophilic		
1.	$\overset{\ominus}{\ddot{C}}H_3$	CH_3MgBr, CH_3Li, $(CH_3)_2Cd$, $(CH_3)_2CuLi$
2.	$\overset{\ominus}{\ddot{P}}h$	PhMgBr, PhLi
3.	$\overset{\ominus}{\ddot{C}}H_2CHO$	CH_3CHO, $\overset{\oplus}{Li}\,\overset{\oplus}{C}\equiv C—OEt$
4.	$\overset{\ominus}{\ddot{C}}H_2COCH_3$	$CH_3COCH_2CO_2Et$, CH_3COCH_3
5.	$\overset{\ominus}{\ddot{C}}H_2CH_2COCH_3$	$CH_2{=}CH—CH(OMe)CH_3$
6.	$\overset{\ominus}{\ddot{C}}H_2CH_2COCH{=}CH_2$	$CH_2{=}CH—CH(OSiMe_3)CH{=}CH_2$
7.	$\overset{\ominus}{\ddot{C}}H_2CO_2H$	$CH_2(CO_2Et)_2$, EtO_2CCH_2CN, $(CH_3CO)_2O$
8.	$\overset{\ominus}{\ddot{C}}H_2CO_2Et$	$BrZnCH_2CO_2Et$
9.		

10.	$\overset{\ominus}{\ddot{C}}H_2CO\overset{\ominus}{\ddot{C}}H_2$	$EtO_2CCH_2COCH_2CO_2Et$
11.	$\overset{\ominus}{\ddot{C}}H_2CH_2COCH_3$	$CH_2{=}CH{-}CH(OCH_3)CH_3$
12.	$CH_3CH{=}\overset{\ominus}{\ddot{C}}H$	$CH_3C\equiv\overset{\ominus}{\ddot{C}}$
13.	$CH_3{-}\overset{\ominus}{\ddot{C}}{=}O$	$HC\equiv\overset{\ominus}{C}\,\overset{\oplus}{Na}$,  $CH_2{=}\overset{Li}{\overset{\vert}{C}}{-}OMe$, 
14.	$\overset{\ominus}{\ddot{C}}OOH$	$:CN^{\ominus}$
15.	$\overset{\ominus}{\ddot{C}}HO$	 , $MeO{-}CH{=}PPh_3$
16.	$\overset{\ominus}{\underset{\ominus}{\ddot{\underset{\cdot\cdot}{C}}}}{=}O$	 , CH_3NO_2
17.	$\overset{\ominus}{\ddot{C}}H_2NH_2$	$:CN^{\ominus}$
18.	‘O’ (nucleophilic)	$H_2O_2/OH^{\ominus}$
19.	$:\ddot{N}H_2^{\ominus}$	 , CH_3CN (Ritter reaction)
20.	$:H^{\ominus}$	$LiAlH_4$, $NaBH_4$, B_2H_6, $Al(Me_2CHO)_3$, $LiAlH(OEt)_3$, $LiAlH(OCMe_3)_3$
21.		CH_3NO_2
22.	$OH{-}\overset{\ominus}{C}H_2$	$MeOCH_2MgCl$
23.	$CH_3\overset{\ominus}{C}HNH_2$	$CH_3CH_2NO_2$

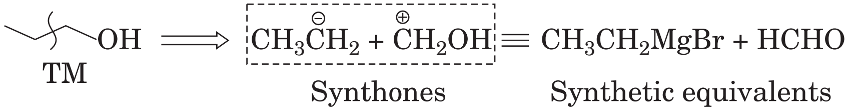
(b) Electrophilic		
1.	$\overset{\oplus}{C}H_3$	CH_3Br, CH_3OTs, CH_3OSO_2Me, $(CH_3)_2SO_4$
2.	$\overset{\oplus}{C}H_2OH$	HCHO
3.	$CH_3\overset{\oplus}{C}HOH$	CH_3CHO
4.	$Me_2\overset{\oplus}{C}OH$	MeCOMe
5.	$\overset{\oplus}{C}H_2COCH_3$	$ClCH_2COCH_3$, $BrCH_2C{\equiv}CH$
6.	$\overset{\oplus}{C}H_2CO_2Et$	$ClCH_2CO_2Et$
7.	$\overset{\oplus}{C}H_2CH_2COCH_3$	$CH_2{=}CH{-}COCH_3$
8.	$\overset{\oplus}{C}H_2CH_2OH$	
9.	$\overset{\oplus}{C}H_2CH_2CH_2OH$	$CH_2{=}CH{-}CHO$, $CH_2{=}CH{-}CO_2Et$
10.	$CH_2{=}\overset{\oplus}{C}H$	$CH_3CH(OEt)_2$
11.	$CH_2{=}\overset{\oplus}{C}OEt$	$CH_3\ C(OEt)_3$
12.	$CH_3{-}\overset{\oplus}{C}{=}O$	CH_3COCl, CH_3CN, CH_3CO_2Et, $(CH_3CO)_2O$
13.	$H{-}\overset{\oplus}{C}{=}O$	$HC(OEt)_3$, HCO_2Et, $CHCl_3/OH^{\ominus}$, $Me_2NCHO/POCl_3$
14.	$\overset{\oplus}{C}H_2{-}NMe_2$	$ClCONMe_2$, $HCHO/Me_2NH/HCOOH$
15.	$CH_3C \equiv \overset{\oplus}{C}$	$CH_3{-}C{\equiv}C{-}Br$
16.	$CH_2{-}\overset{\oplus}{C}{=}O$	$ClCH_2COCl$
17.	$\overset{\oplus}{C}H_2{-}\overset{\oplus}{C}H_2$	$BrCH_2CH_2Br$
18.	$\overset{\oplus}{\underset{\oplus}{C}}H_2$	CH_2Br_2, HCHO

19.	$\overset{\oplus\oplus\oplus}{CH}$	$HC(OEt)_3$
20.	$\overset{\oplus}{\underset{\oplus}{C}}{=}O$	$O{=}C(OEt)_2$, $COCl_2$
21.	$\overset{\oplus}{C}OOH$	CO_2, $ClCO_2Et$
22.	$O{=}\overset{\oplus}{C}{-}CH_2\overset{\oplus}{C}{=}O$	$EtO_2CCH_2CO_2Et$
23.	$O{=}\overset{\oplus}{C}CH_2CH_2\overset{\oplus}{C}{=}O$	
24.	$CH_3CH_2O\overset{\oplus}{C}H_2$	$CH_3CH_2OCH_2Cl$
25.	'O' (electrophilic)	CF_3CO_2OH, m-$ClC_6H_4CO_2OH$, $H_2O_2/OH^{\ominus}$
26.	$\overset{\oplus}{C}N$	Cl—CN
27.	$\overset{\oplus}{S}O_3H$	conc. H_2SO_4
28.	$\overset{\oplus}{S}O_2Cl$	$ClSO_3H$
29.	$\overset{\oplus}{N}H_2$	NH_2Cl, NH_2OCH_3
30.	$\overset{\oplus}{Cl}$	Cl_2, $Cl_2/FeCl_3$
31.	$\overset{\oplus}{N}O_2$	conc. HNO_3 + conc. H_2SO_4, $AcONO_2$, N_2O_5
32.	$\overset{\oplus}{N}O$	$NaNO_2/HCl$ (HNO_2)
(c) Mixed Electrophilic and Nucleophilic		
1.	$\overset{\oplus}{\underset{\ominus}{C}}H_2$	CH_2N_2, CH_2SMe_2, CH_2PPh_3, $CH_2(I)ZnI$
2.	$\overset{\oplus}{\underset{\ominus}{C}}{=}O$	$Me_3C{-}N{=}C{:}$
3.	$\overset{\ominus}{C}H_2{-}\overset{\oplus}{C}{=}O$	$CH_2(CO_2Et)_2$, ClMg 

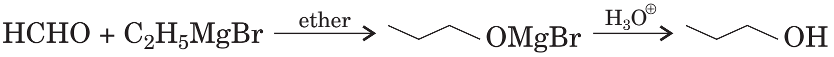
4.	$\overset{\ominus}{C}H_2CH_2CH_2\overset{\oplus}{C}H_2$	$(EtO_2C)_2CHCH_2CH_2CH_2Br$
5.	$\overset{\ominus}{C}H_2CH_2CH_2CH_2\overset{\oplus}{C}{=}O$	 $EtO_2C\,CH_2CH_2CH_2CH_2{-}\overset{O}{\overset{\Vert}{C}}{-}OEt$
6.	 $\overset{\ominus}{C}H_2{-}\overset{O}{\overset{\Vert}{C}}{-}CH_2CH_2CH_2{-}\overset{\oplus}{C}{=}O$	$CH_3COCH_2CH_2CH_2CO_2Et$

Examples of retrosynthetic analysis and the designated synthesis of some target molecules (TM) to show the applications of various types of synthones and synthetic equivalents listed in Table 3.1.

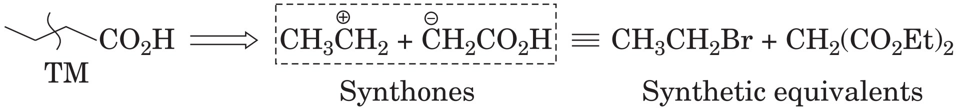
1. *Retrosynthetic analysis*


OH
TM
$CH_3\overset{\ominus}{C}H_2 + \overset{\oplus}{C}H_2OH$
$\equiv CH_3CH_2MgBr + HCHO$
Synthones
Synthetic equivalents

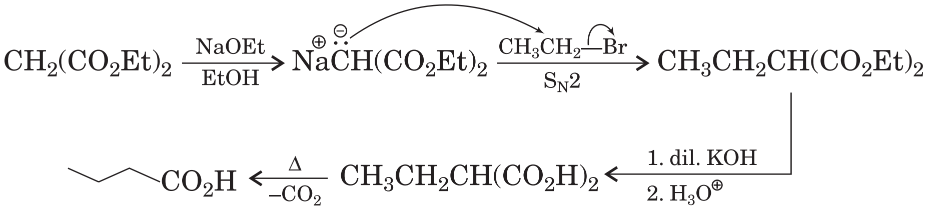
Synthesis



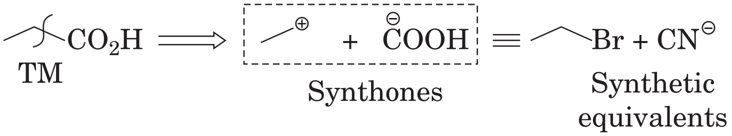
2. *Retrosynthetic analysis*


CO_2H
TM
$CH_3\overset{\oplus}{C}H_2 + \overset{\ominus}{C}H_2CO_2H$
$\equiv CH_3CH_2Br + CH_2(CO_2Et)_2$
Synthones
Synthetic equivalents

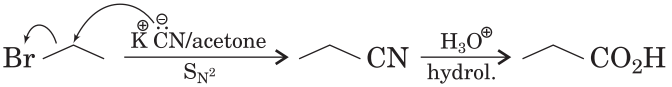
Synthesis



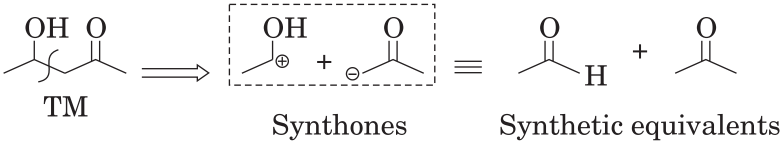
3. *Retrosynthetic analysis*



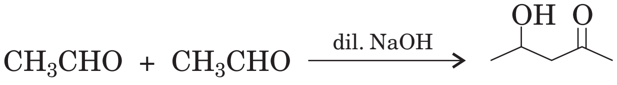
Synthesis



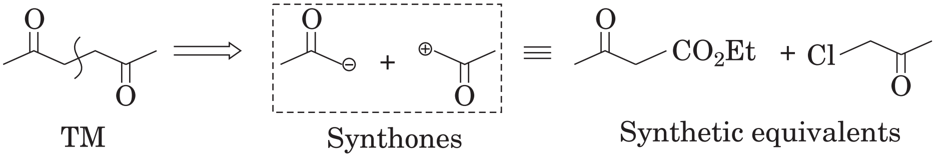
4. *Retrosynthetic analysis*



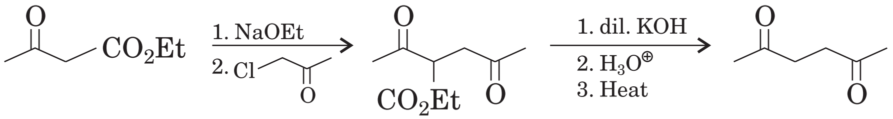
Synthesis



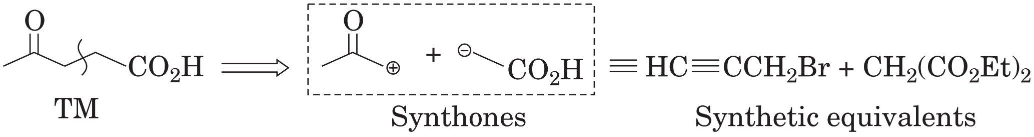
5. *Retrosynthetic analysis*



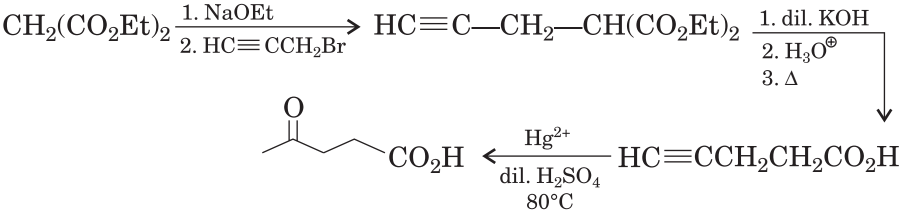
Synthesis



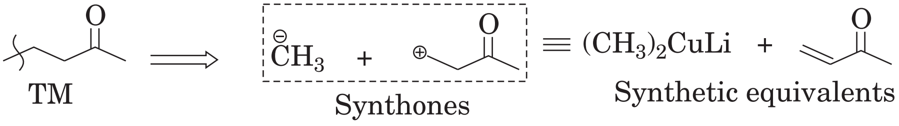
6. *Retrosynthetic analysis*



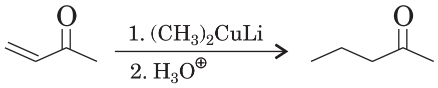
Synthesis



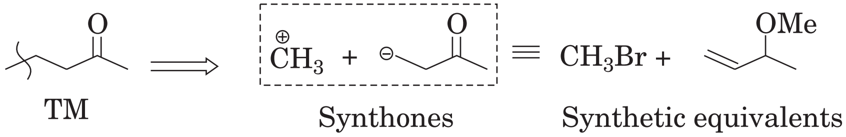
7. *Retrosynthetic analysis*



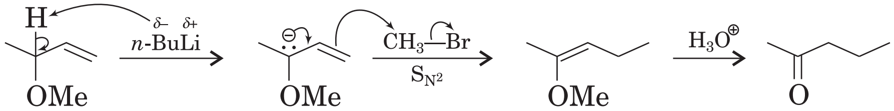
Synthesis



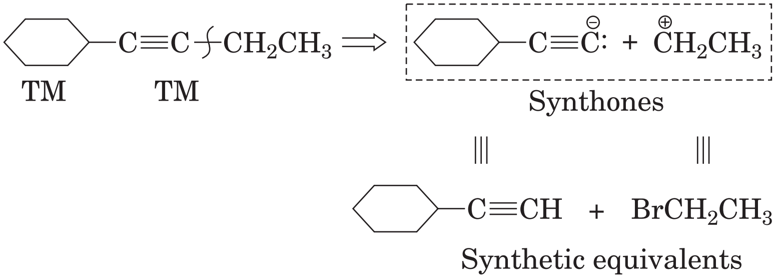
8. *Retrosynthetic analysis*



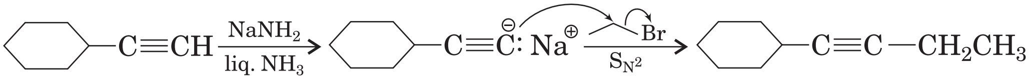
Synthesis



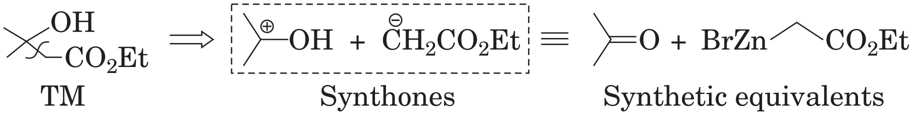
9. *Retrosynthetic analysis*



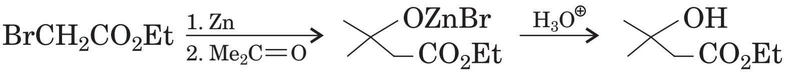
Synthesis



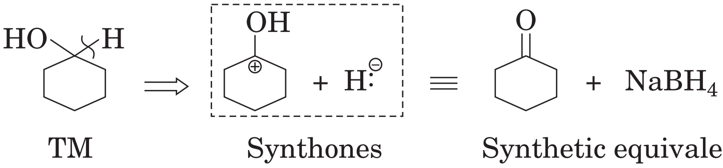
10. *Retrosynthetic analysis*



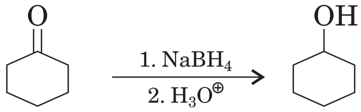
Synthesis



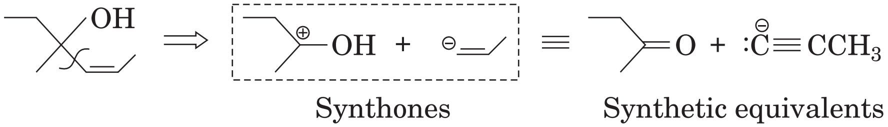
11. *Retrosynthetic analysis*



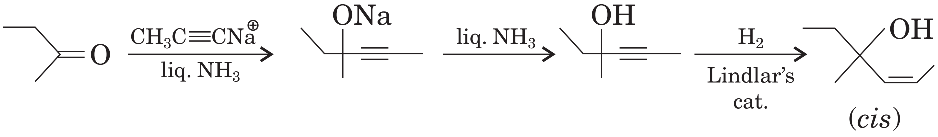
Synthesis



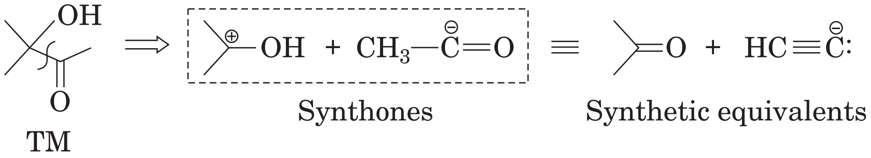
12. *Retrosynthetic analysis*



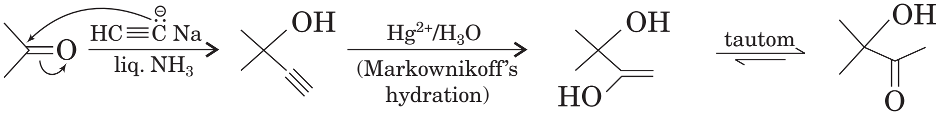
Synthesis



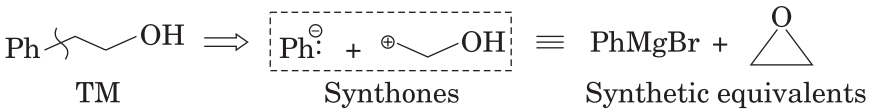
13. *Retrosynthetic analysis*



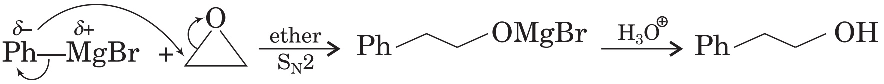
Synthesis



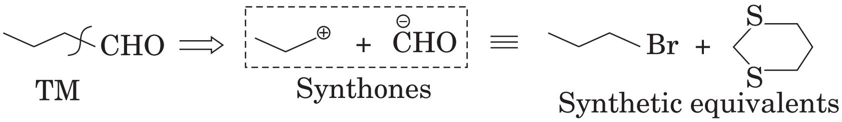
14. *Retrosynthetic analysis*



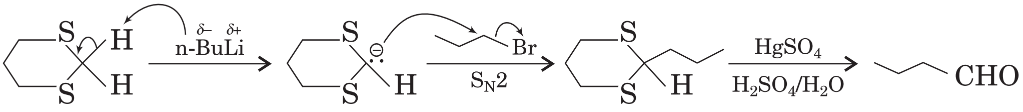
Synthesis



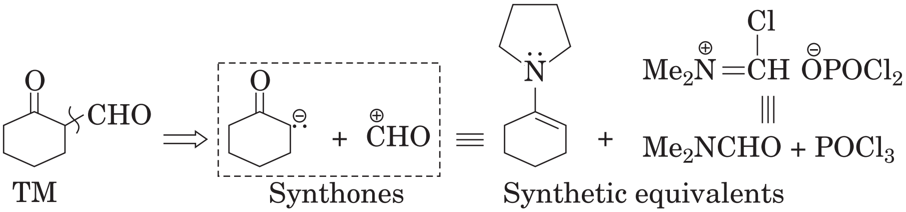
15. *Retrosynthetic analysis*



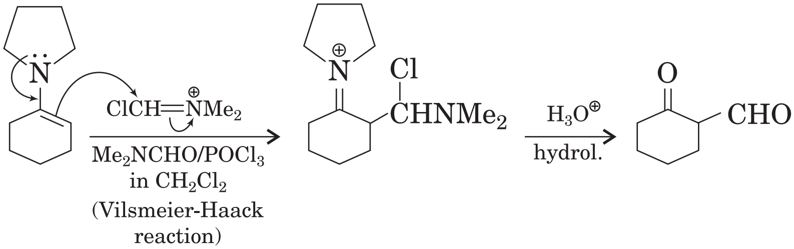
Synthesis



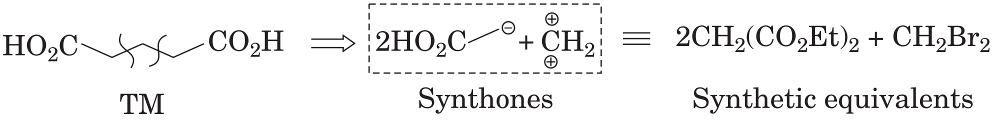
16. *Retrosynthetic analysis*



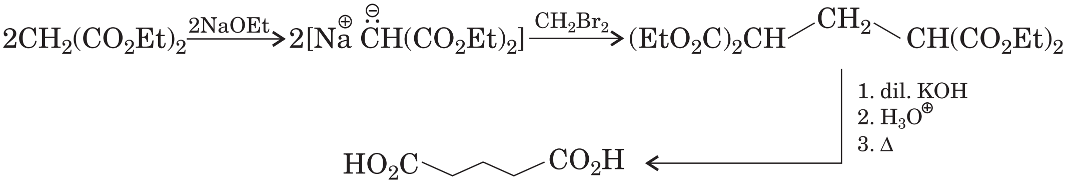
Synthesis



17. *Retrosynthetic analysis*



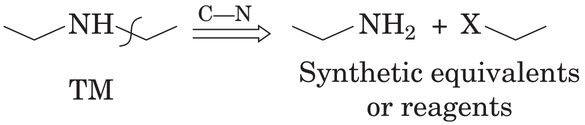
Synthesis



3.1.1.7 Functional Group Interconversion

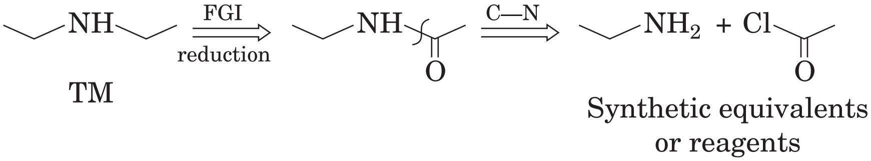
The operation of writing one functional group for another so that the disconnection of the strategic bond becomes easier is called *functional group interconversion* or *FGI*. It is, in fact, the reverse of a chemical reaction involving oxidation, reduction, substitution, addition and elimination.

Example 1

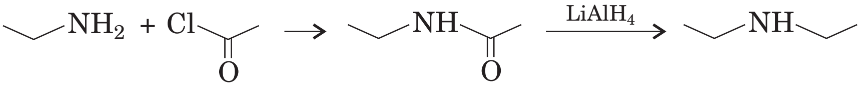


Since the TM is a 2° amine, it is usually more reactive the starting 1° amine $EtNH_2$ and there is a danger of multiple alkylation (the electron density on N atom increases due to presence of one additional alkyl group). FGI is used to overcome this problem. The reactive amine is converted to a less reactive amide before disconnection. Since the reduction of amide to amine is quite reliable, therefore, FGI is a reasonable one.

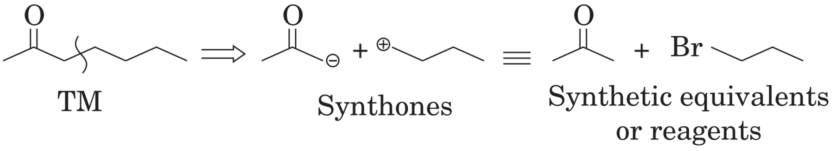
Retrosynthetic analysis



Synthesis

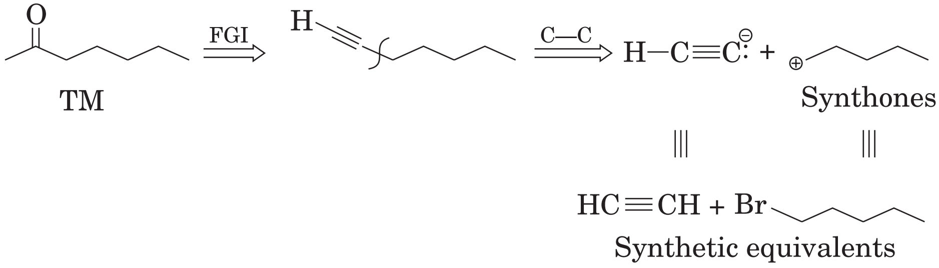


Example 2

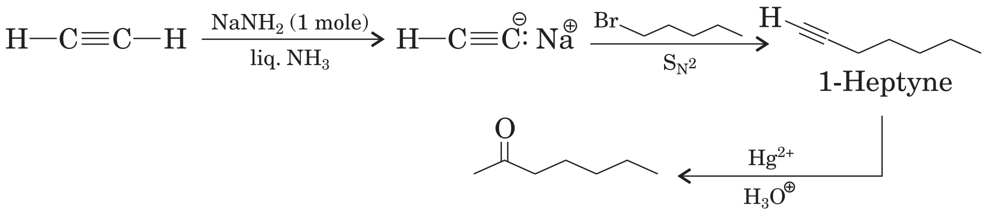


Therefore, the enolate of acetone may be allowed to react with 1-bromobutane (S_N2) to give the TM. Although the direct alkylation of acetone enolate with 1-bromobutane looks attractive, one condition for the success of the reaction is to convert acetone quickly and completely to the enolate to avoid self-condensation with any ketone left unreacted. LDA can be used for this purpose, but working with the base also attended with several difficulties (in addition to its high cost). FGI is used to avoid these difficulties. The $—CHCH_3$ group is converted to a $—C\equiv CH$ group before disconnection. Since the acid-catalyzed hydration of $—C\equiv CH$ to give $—COCH_3$ is quite reliable, therefore, FGI is a reasonable one. Also, $HC\equiv\overset{\ominus}{C}:$ is a good nucleophile.

Retrosynthetic analysis



Synthesis



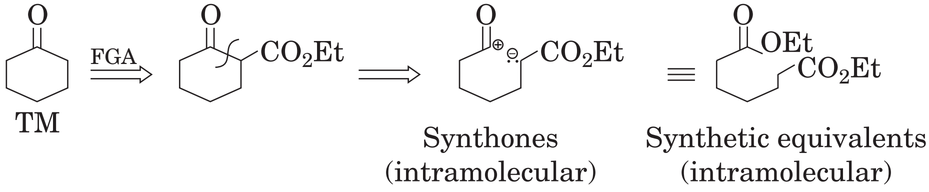
We need not always write the synthones first and then the synthetic equivalents (reagents). If the regents are simple, they can be written directly.

3.1.1.8 Functional Group Addition

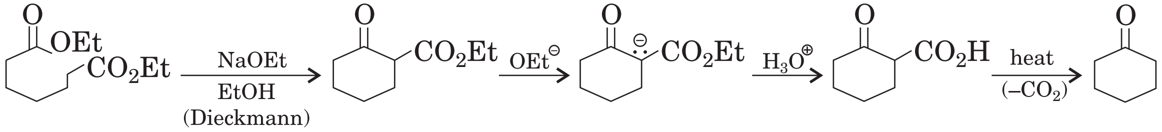
When a retrosynthetic analysis is done for a TM, it is often required to add a functional group either to the TM or to any of the intermediates to get an appropriate synthon and its equivalent which can be utilized in a known reliable reaction. It is to be noted that the functional group which is to be added to give the right synthon must be removed readily. In the following examples, we can understand the purpose of FGA.

Example 1

Retrosynthetic analysis



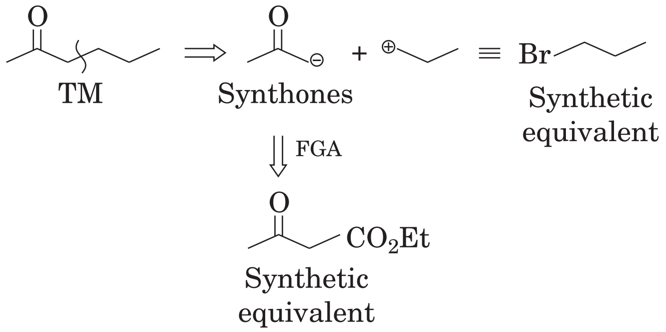
Synthesis



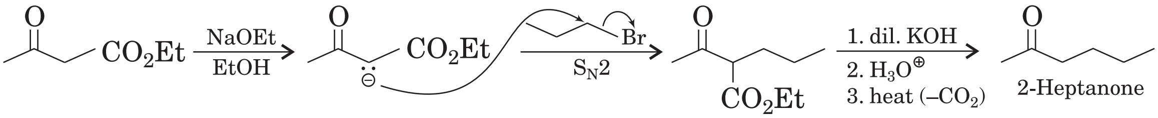
Since the α-C of an ester can readily form a carbanion and the —CO_2Et group (β to a carbonyl group) can be removed easily by hydrolysis followed by decarboxylation, the —CO_2Et group is added to the TM in the first step of analysis.

Example 2

Retrosynthetic analysis



Synthesis



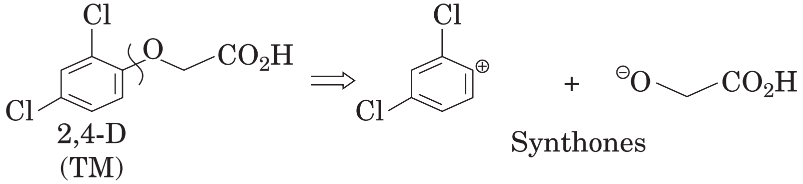
In the first example, disconnection is done after FGA, i.e., the functional group is added to the TM, and in the second example, disconnection is done before FGA, i.e., the functional group is added to the synthon.

3.1.2 Guidelines for Choosing Suitable Disconnections

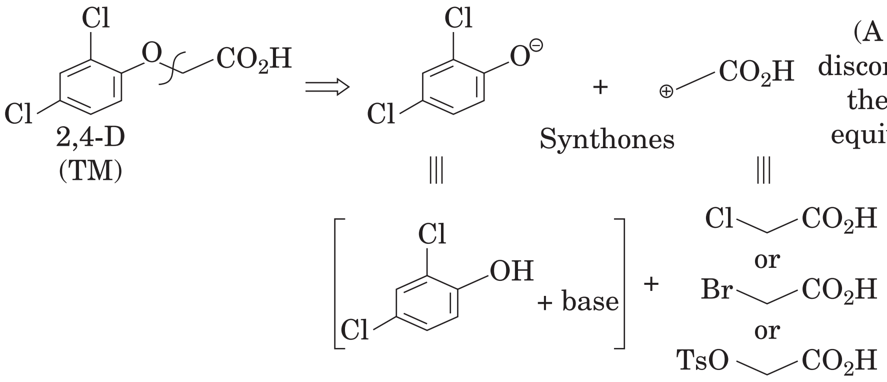
The hardest task in designing a retrosynthetic analysis is to spot the strategic bond where disconnection is to be made. The following are the guidelines for choosing disconnection.

Guideline 1: *Disconnections must correspond to known reliable (workable) reactions.*

For every disconnection, there must be a reliable reaction in our mind for effecting the corresponding reconnection (bond formation) during the actual forward synthesis of the target molecule. For example, when the ether 2,4-D (a herbicide) is taken for disconnection, the strategic bond to be disconnected is O—C$_{sp3}$ because the synthesis of ether is known to us. The O—C$_{sp2}$ bond should not be disconnected because no reliable reaction corresponding to nucleophilic attack of an alcohol on an unactivated aromatic ring is known to us.



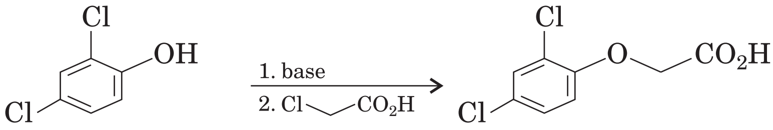
(A bad choice for disconnection because there is no reliable equivalent reaction)



(A good choice of disconnection because there is a reliable equivalent reaction)

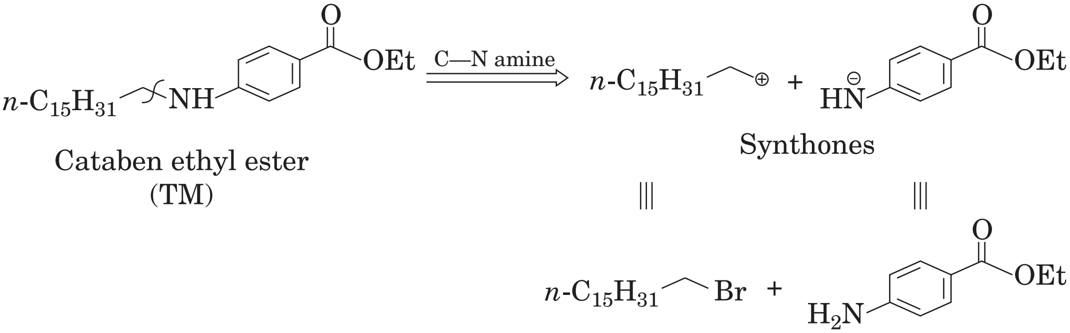
Synthetic equivalents or reagents

Synthesis



Guideline 2: *When two parts of a compound is found to be joined by a heteroatom, disconnection is to be made next to the heteroatom.*

This guideline works for esters, amides, ethers, amines, acetals, sulfides and so on, because these compounds are often synthesized by a substitution reaction. Using Guideline 2, a disconnection next to the N atom cataben ethyl ester (a precursor to a drug used for lowering blood lipid level) can be suggested. Again, according to the first guideline, disconnection is to be made on the alkyl and not on the aryl side.

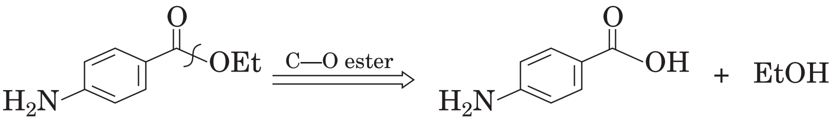


Cataben ethyl ester
(TM)

Synthones

Synthetic equivalents
or reagents

Although the alkyl bromide is available, we have to prepare the aromatic amino-ester and the best disconnection for an ester is the C—O bond between the carbonyl carbon and the oxygen of the esterifying group.

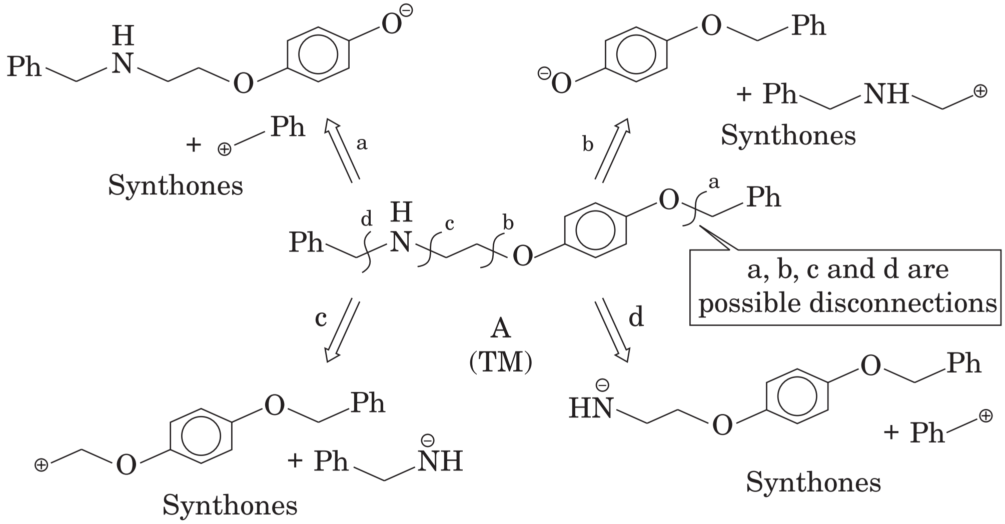


Guideline 3: *Alternate disconnections are to be considered and the routes that avoid chemoselectivity problems are to be chosen. This can often be done by disconnecting more reactive groups first.*

When one functional group within a molecule reacts leaving other potentially reactive functional group(s), unaltered is called a *chemoselective reaction*. Thus, when a molecule contains two reactive functional groups and we want one of them to react, the problem of chemoselectivity arises.

The following compound (A) is an intermediate involved in the synthesis of IClI-D7114 (a potential anti-obesity drug). This compound with two ethers and an amine functional group requires four reasonable disconnections to take it back to available starting materials and these are one at each ether groups (a and b) or on either side of amine N atom (c and d). We have to find out the best one.

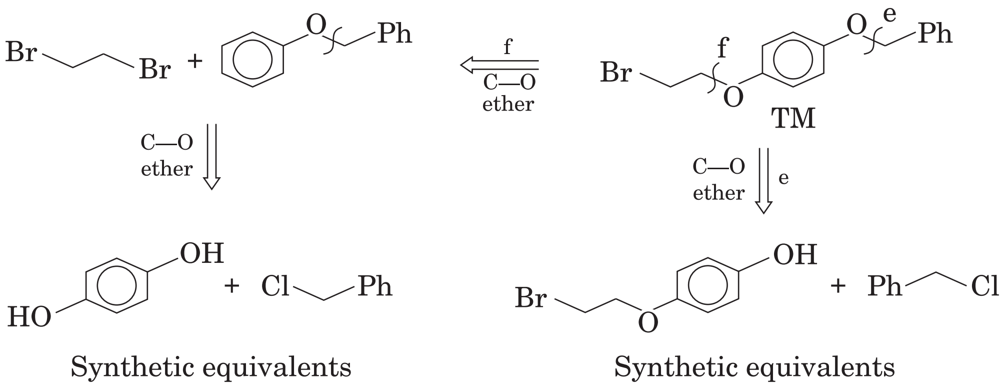
Retrosynthetic analysis of ICI-D7114 intermediate



Both (a) and (b) disconnections pose problems of chemoselectivity as it would be difficult to alkylate phenol selectively in the presence of the basic nitrogen atom. Between (c) and (d), (c) appears to be the better choice because the next disconnection after (d) will have to be an alkylation of O in the presence of an —NH_2 group and thus causes chemoselectivity problem.

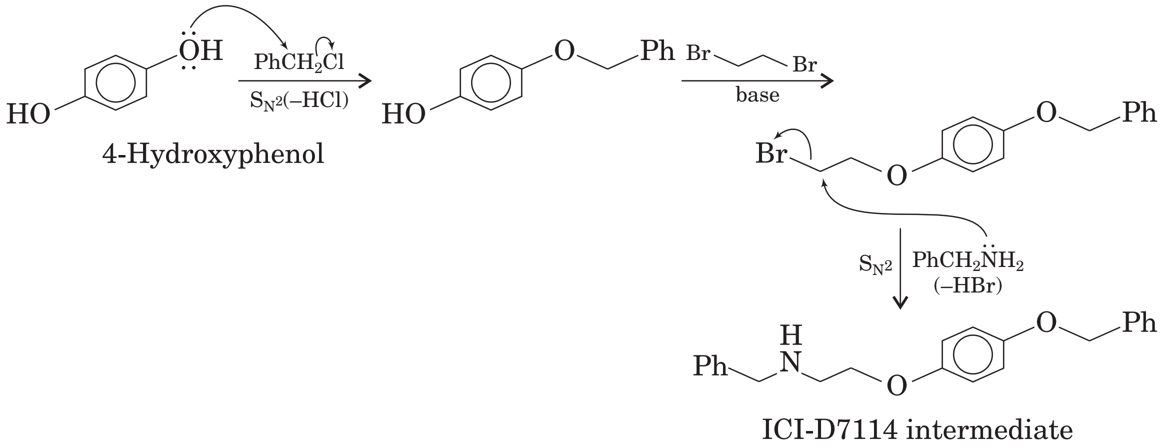
To avoid the chemoselectivity problems like this, more reactive groups should be introduced late in the synthesis, i.e., they should be disconnected first.

This guideline is helpful in the next retrosynthetic step. Disconnection (c) leads to a compound with two ethers that might be disconnected further by disconnection (e) or (f).



Disconnection (e) requires alkylation of a compound which itself is an alkylating agent. Disconnection (f) is much more satisfactory because this leads to 1,2-dibromethane and to a compound that is easily disconnected to 4-hydroxyphenol and benzyl chloride. Using the Guideline 3, we can say that it is better to disconnect the bromoethyl group (f) before the benzyl group because the bromoethyl group is more reactive and more likely to cause chemoselectivity problems.

Synthesis of ICI-D7114 intermediate



ICI-D7114 intermediate
(TM)

3.1.3 Guidelines for the Order of Events in the Synthesis of Aromatic Compounds

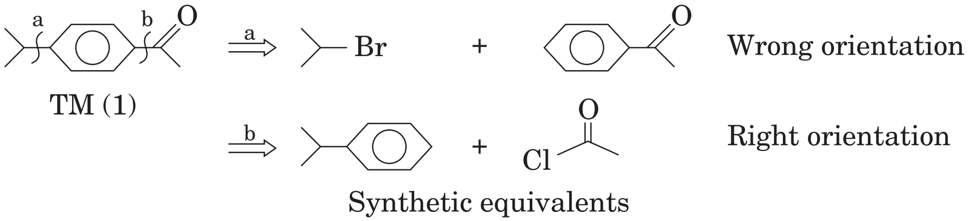
In designing a synthesis of a TM, there are many possible steps which are to be followed one after another. The order in which a set of reactions (events) is carried out to get the TM is called the order of events.

The general guidelines (based on directing influence and activation) for the order of events are as follows:

Guideline 1: *The relationship between the groups are to be examined, looking for groups which direct to the right position. For doing this, all the groups are to be disconnected, in* *turn and the reverse reactions are to be examined if they would give right orientations.*

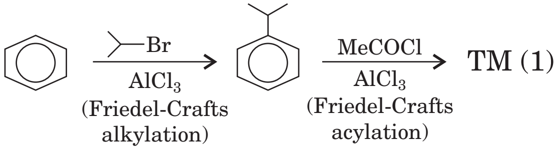
The retrosynthetic analysis of the orris odour ketone (1) could be tackled by two possible first disconnections.

Retrosynthetic analysis



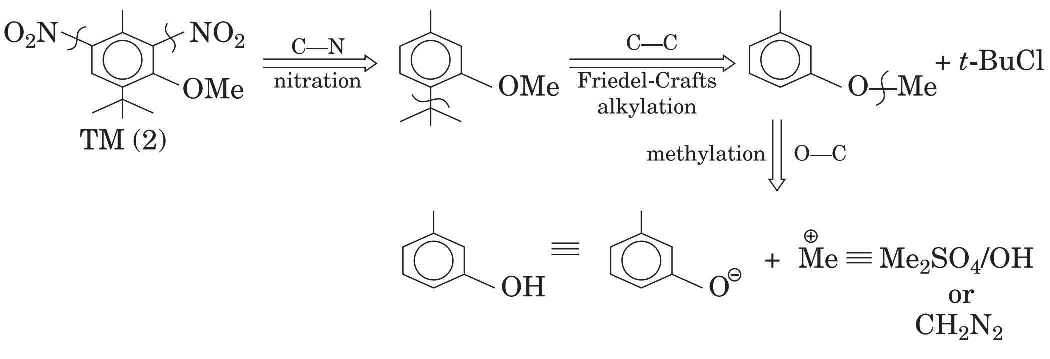
In the TM, the groups are *para* to each other. Since the alkyl group is *o*, *p*-directing the disconnection (b) gives starting materials which would react in the right orientation to give the TM. The disconnection (a) gives starting materials which would react in the wrong orientation because the carbonyl group is *meta* directing. Therefore, the correct order of events in this synthesis should be alkylation followed by acylation but not the reverse.

Synthesis

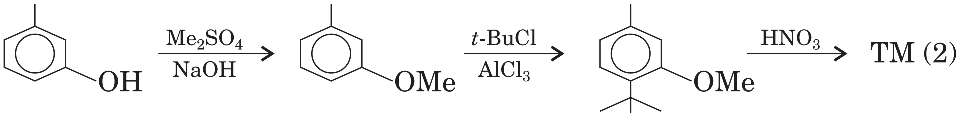


Guideline 2: If there is a choice, the most electron-attracting substituents is to be disconnected first (i.e., to be added last) and this is because it is normally difficult to introduce any other substituent in the presence of this deactivating substituent. The —NO_2 groups in the musk ketone (2), for example, are by far the most electron-attracting. Therefore, these should be disconnected first. Now, the Me or the *t*-Bu group can be added by Friedel-Crafts alkylation. Since the —OMe group is strongly *o*, p-directing, the *t*-Bu group is to be disconnected. The aromatic compound obtained by disconnection is the methyl ether of readily available *m*-cresol and can be prepared by methylating with Me_2SO_4, CH_2N_2, etc.

Retrosynthetic analysis



Synthesis



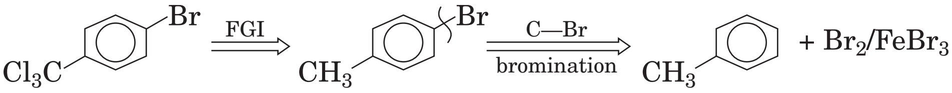
Guideline 3: If FGI is required during synthesis, it may well after the directing effect of the substitutent. The other substituents may, therefore, be added either before or after the FGI. Some examples are as follows:

o, p-directing —Me $\longrightarrow$ —COOH, —CCl_3 or —CF_3 m-directing

m-directing —NO_2 $\longrightarrow$ —NH_2 o, p-directing

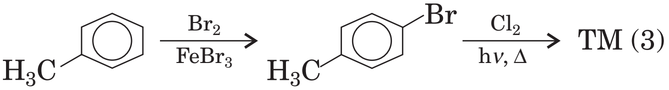
The synthesis of the compound (3) involves bromination of the ring and chlorination of the methyl group (FGI). Since the —CCl_3 group in m-directing, the aryl bromide is to be disconnected after FGI.

Retrosynthetic analysis



TM (3)

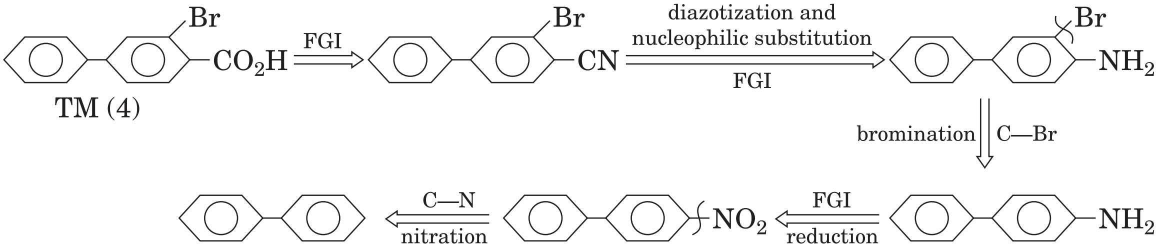
Synthesis



Guideline 4: Many groups can be added by nucleophilic substitution on a diazonium salt, prepared from an amine. Since the amine group is strongly o, p-directing, therefore, adding other groups at the amine stage may be advisable.

Let us consider the synthesis of the acid (4). Since the other benzene ring is o, p-directing, to introduce bromine *meta* to —Ph the —COOH group must be replaced by —NH_2, a more powerful o, p-directing group than —Ph.

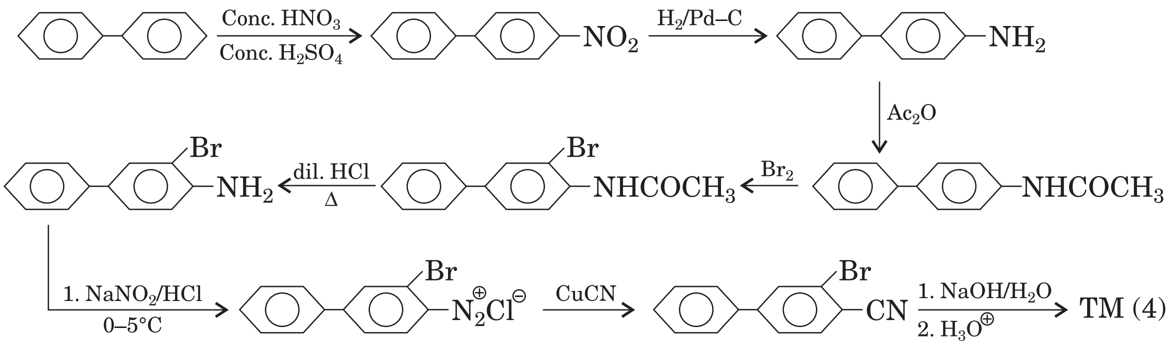
Retrosynthetic analysis



TM (4)

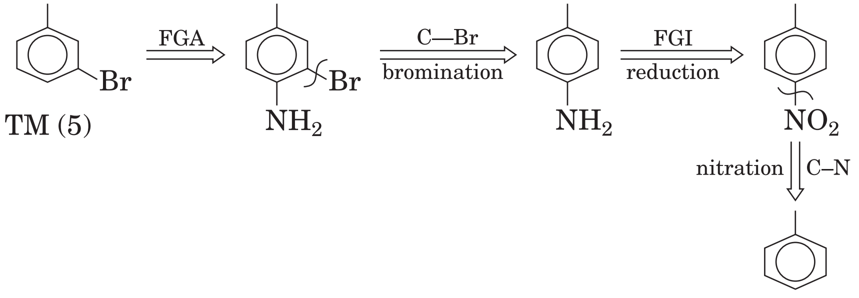
In this synthesis, acetylation of the amino group is necessary to prevent over

Synthesis

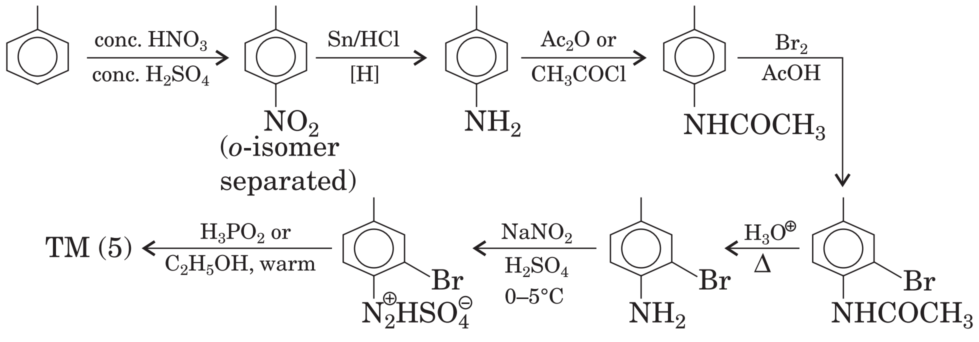


Guideline 5: When two *o*, *p*-directing groups are to be placed *meta* to each other, a 'dummy' amino group is to be introduced, and after setting up the required relationship, it is to be removed by diazotization and reduction. Let us, for example, design a synthesis of the compound (5) from toluene.

Retrosynthetic analysis

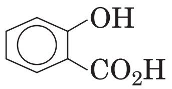


Synthesis

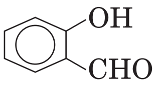


Guideline 6: A good synthetic strategy is not to disconnect the substituent which are difficult to introduce. In that case, it is better to use a starting material containing such a substituent, e.g., —OH, —OR, etc. This guideline is already followed for compound (2) (substituent —OMe) and for compound (4) (substituent Ph).

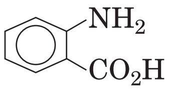
Guideline 7: For a target molecule with difficult combination of substituents, a readily available starting material is to be looked for. For example:



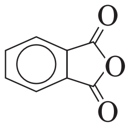
Salicylic acid



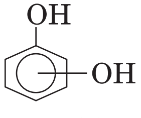
Salicylaldehyde



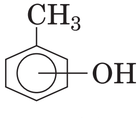
Anthranilic acid



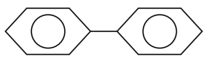
Phthalic anhydride

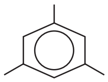


o-, *m*- or *p*-Dihydroxybenzene



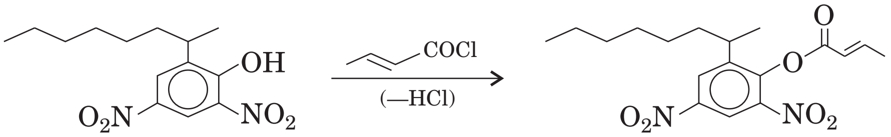
o-, *m*- or *p*-Cresol


Biphenyl


Mesitylene

Guideline 8: Sequences leading to unwanted reactions at other sites in the molecule should be avoided. For example, nitration of benzaldehyde gives only 50% *m*-nitrobenzaldehyde since nitric acid oxidises —CHO to —COOH. One can easily overcome this problem by nitrating benzoic acid followed by reducing the —COOH group to —CHO.

Guideline 9: If *o*, *p*-substitution is involved, separation of isomers may be avoided by blocking one position. For example, let us design a synthesis for the compound (6) which is used of prepare the garden fungicide Dinocap.

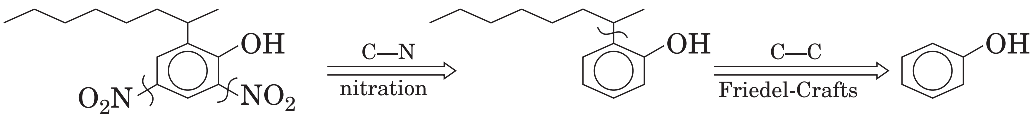


TM (6)

Dinocap

If the nitro groups are disconnected first (guideline 2), the Friedel-Crafts alkylation required to introduce the relatively bulky alkyl group (1-methylheptyl) would give mostly the para product (—OH group is *o*, *p*-directing).

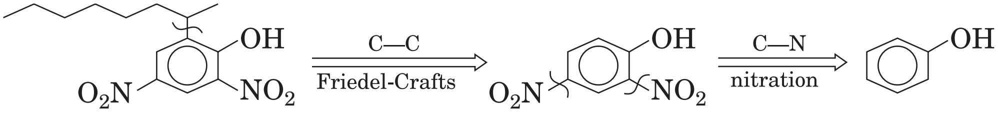
Retrosynthetic analysis 1



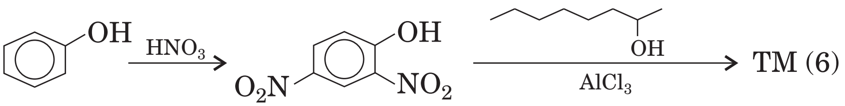
TM (6)

The alternative order of events, disconnecting the alkyl group first, is unusual but sensible because the *para* position (with respect to —OH) is blocked.

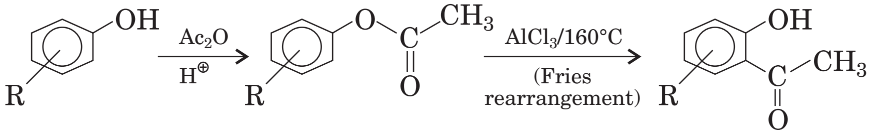
Retrosynthetic analysis 2

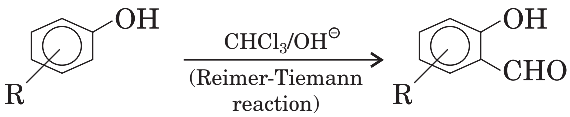


Synthesis



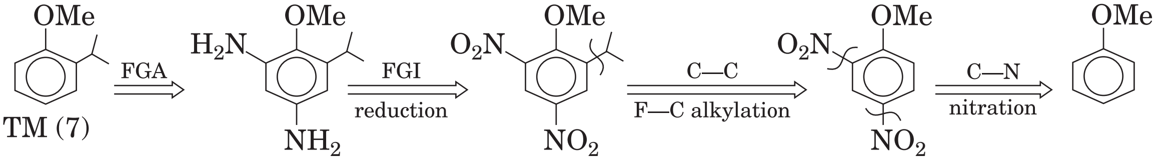
Large amounts of *ortho* product can be obtained by the reactions like the Fries rearrangement and the Reimer–Tiemann reaction. These reactions can, therefore, be used to set up *ortho* substituents with other substituents present but one —OH group is to be present in the molecule.



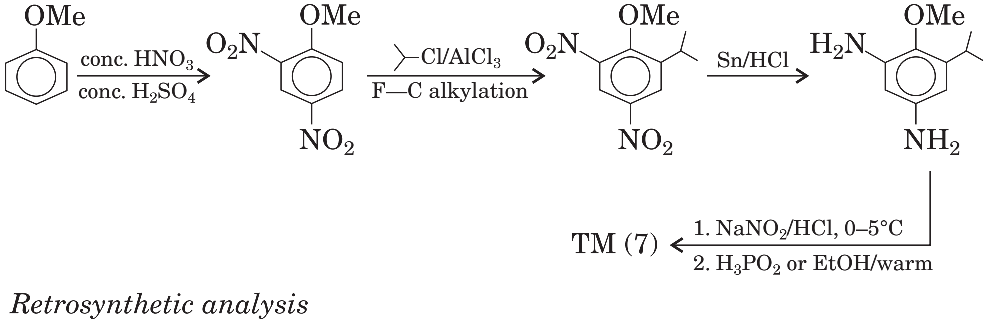


Retrosynthetic Analysis and Synthesis of Some Benzoid TMs Using Disconnection Approach

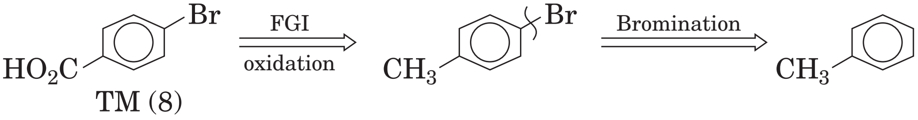
1. *Retrosynthetic analysis*



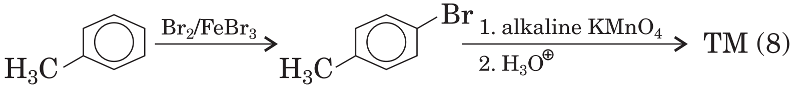
Synthesis



2. *Retrosynthetic analysis*

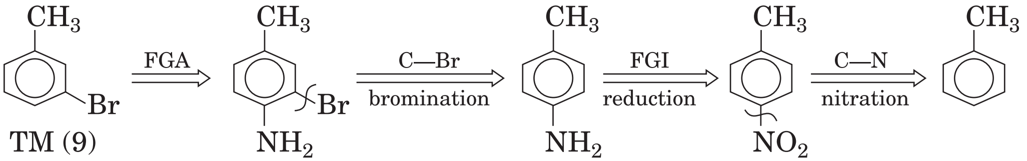


Synthesis

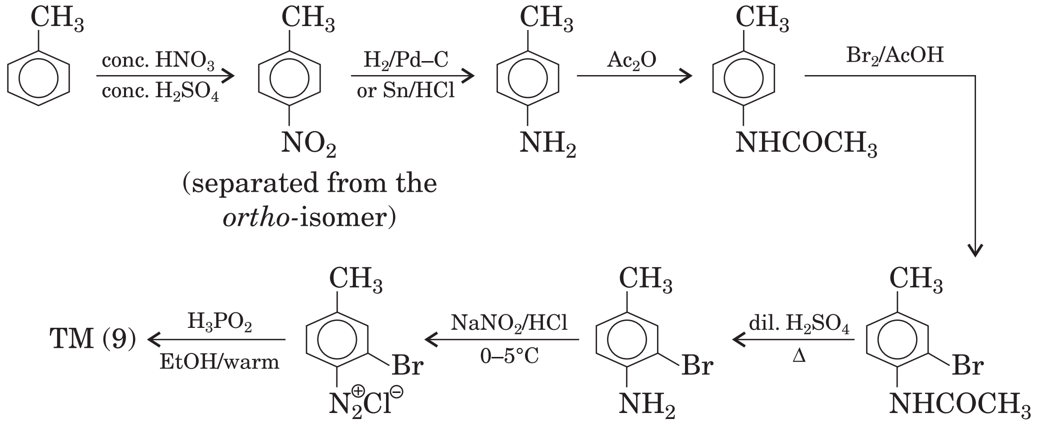


The order of events must not be the reverse because the —COOH group is *m*-directing.

3. *Retrosynthetic analysis*

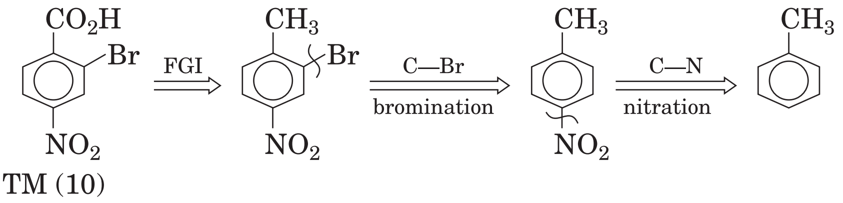


Synthesis



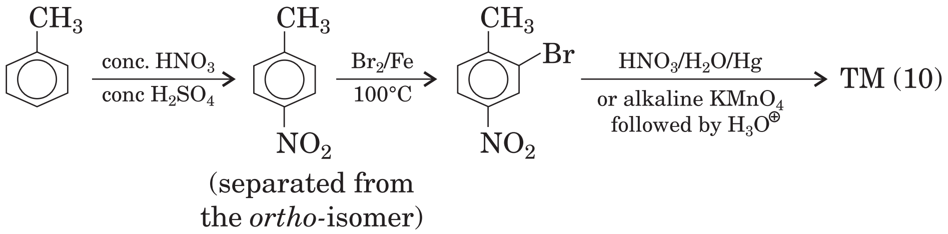
These two *o*, *p*-directing groups are placed *meta* to each other with the help of a 'dummy' amino group.

4. *Retrosynthetic analysis*



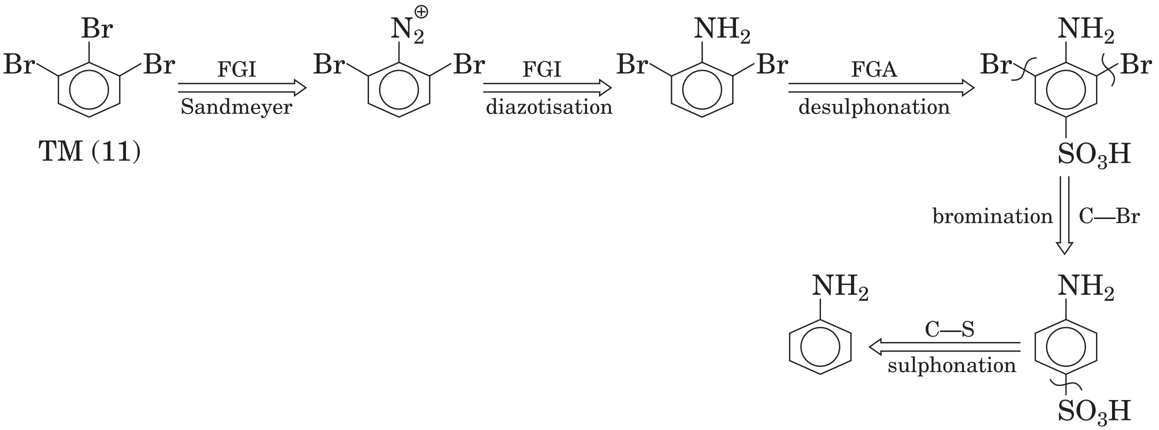
Disconnection of —Br before —NO_2 creates no problem because —CH_3 is *o*, *p*-directing and —NO_2 is *m*-directing. Their combined effect will give only one bromo derivative. However, if —NO_2 is disconnected first, nitration of *o*-bromotoulene is to be carried out and a mixture of products would have been obtained since both the groups are *o*, *p*-directing.

Synthesis



(separated from the *ortho*-isomer)

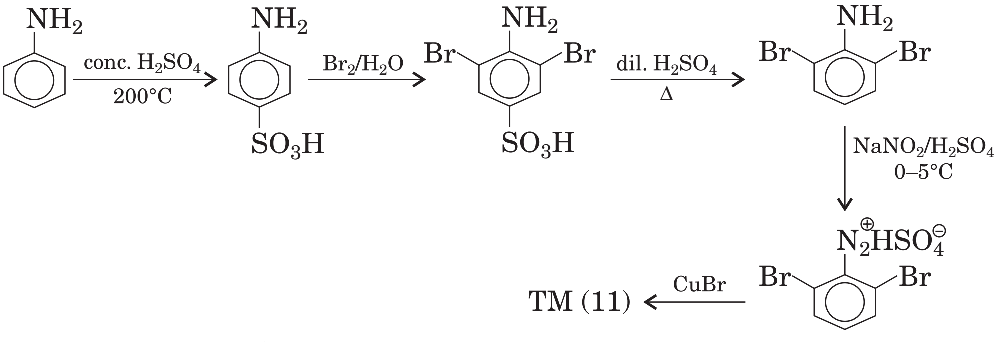
5. *Retrosynthetic analysis*



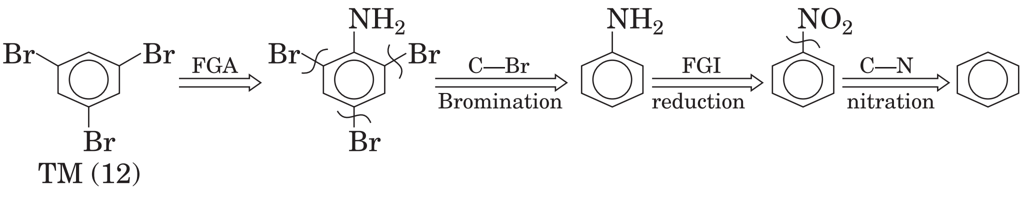
TM (11)

FGI is to be done to change the middle bromine into an —NH_2 group because it helps to produce other bromines *ortho* to it (when the *para*-position in temporarily blocked).

Synthesis



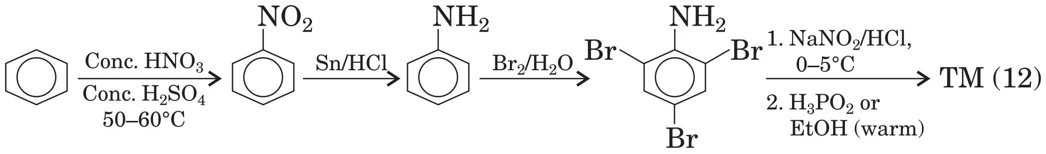
6. *Retrosynthetic analysis*



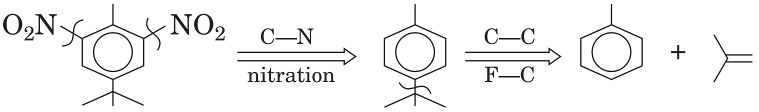
TM (12)

An —NH_2 group is to be added (by nitration followed by reduction) for placing three Br atoms *meta* to each other through bromination.

Synthesis



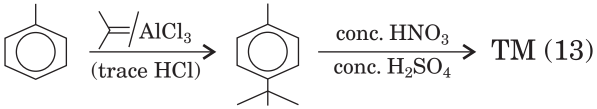
7. *Retrosynthetic analysis*



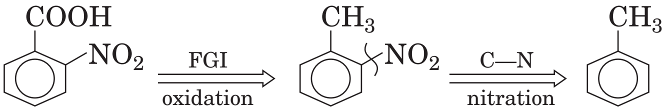
TM (13)

The electron-withdrawing (deactivating) —NO_2 groups are disconnected first because the Friedel-Crafts alkylation of the ring containing two —NO_2 groups is not possible.

Synthesis



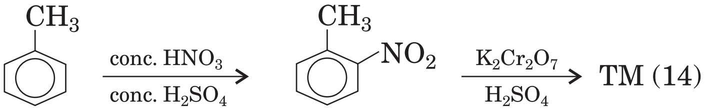
8. *Retrosynthetic analysis*



TM (14)

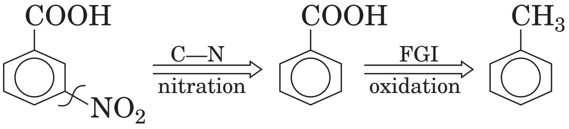
The directing effect of the methyl group is to be used to prepare the TM and so, nitration is carried out before oxidation.

Synthesis



(separated from
the *para*-isomer)

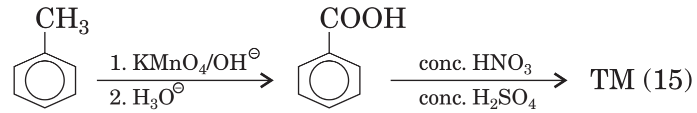
9. *Retrosynthetic analysis*



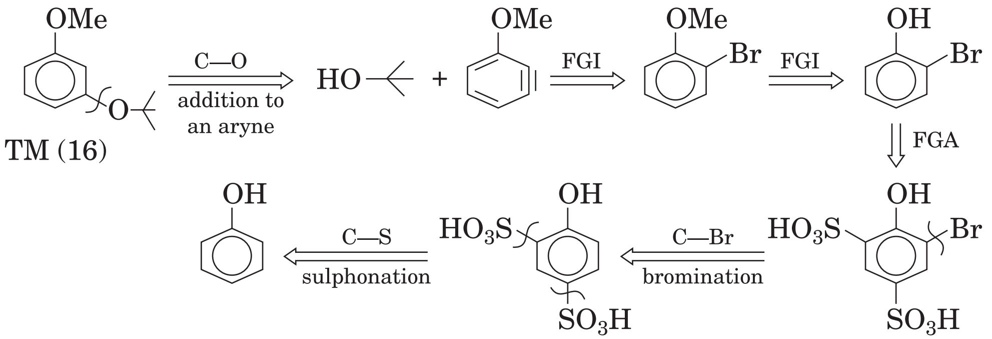
TM (15)

The directing effect of the —COOH group is to be used to prepare the TM and so, oxidation is carried out before nitration.

Synthesis

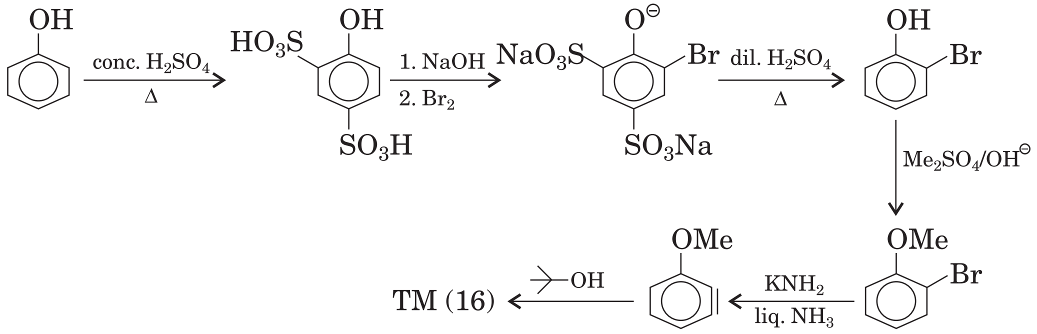


10. *Retrosynthetic analysis*



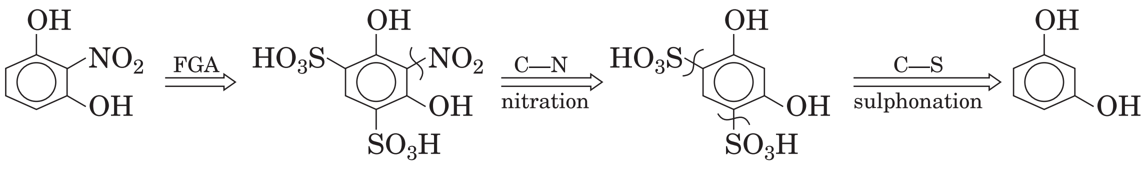
To introduce one Br atom *ortho* to —OH, the other *ortho* position and the *para*-position are blocked by sulphonation and after the purpose is solved, the —SO_3H groups are removed.

Synthesis

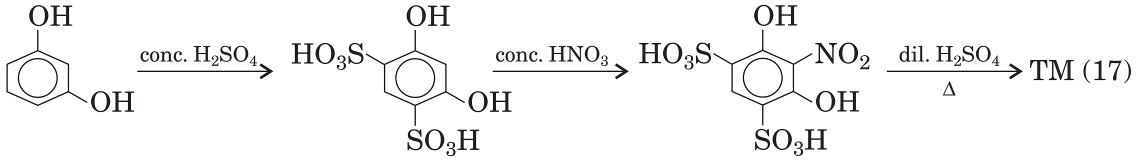


Due to electron-attracting –I effect of the —OMe group, attack by *tert*-butyl alcohol occurs preferably at the meta-position to give the target molecule.

11. *Retrosynthetic analysis*

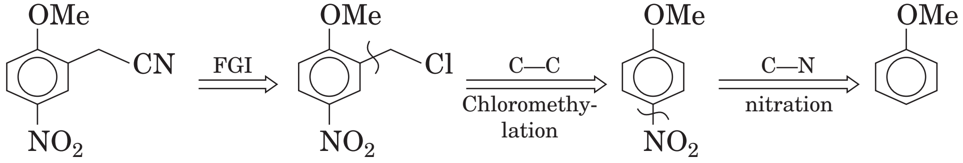


Synthesis



One *ortho*- and the *meta*-position with respect to both the —OH groups are blocked by sulphonation. As a consequence, the —NO_2 group is compelled to enter into the *ortho*-position flanked by the two —OH groups.

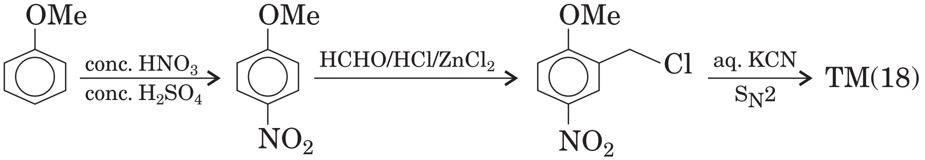
12. *Retrosynthetic analysis*



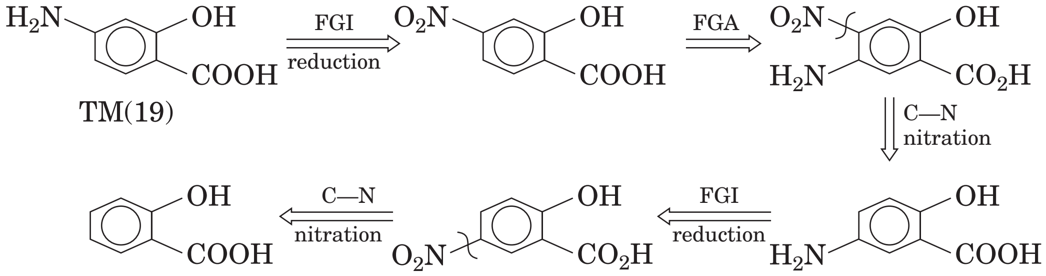
TM (18)

The —NO_2 group should not be disconnected first because mixed acid oxidises —CH_2Cl to —COOH.

Synthesis



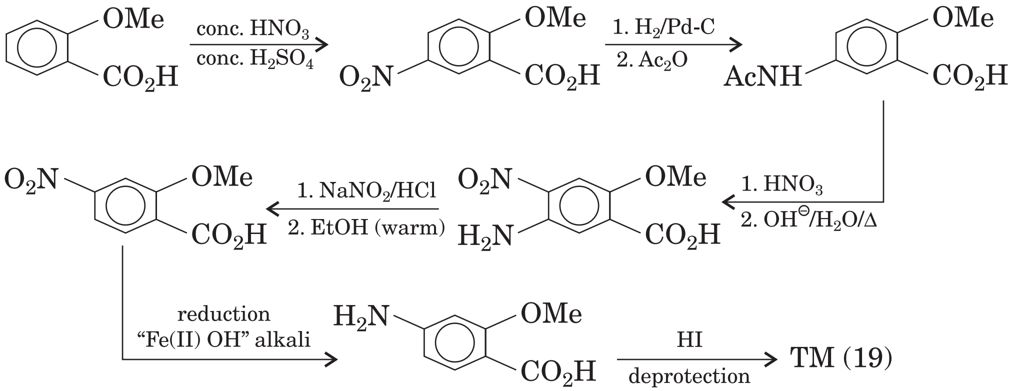
13. *Retrosynthetic analysis*



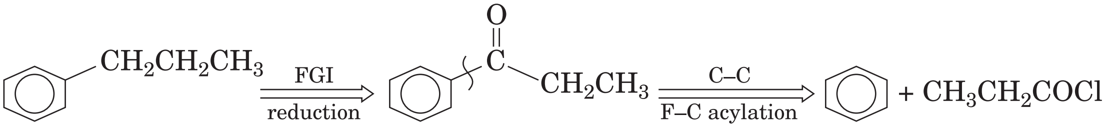
TM(19)

It is better to start the synthesis with salicylic acid in which the hydroxyl group is protected by alkylation (to avoid oxidation at the nitration stage).

Synthesis



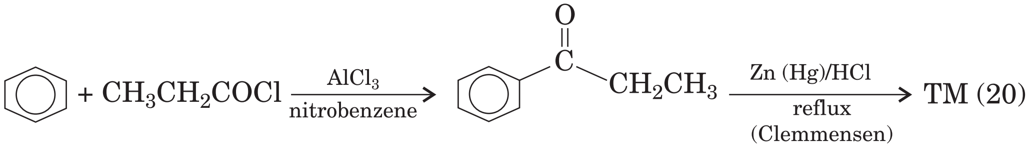
14. *Retrosynthetic analysis*



TM (20)

Alkylation of benzene using *n*-propyl chloride produces isopropylbenzene as the major product due to rearrangement. Also, we cannot avoid polyalkylation. For this reason, we have to prepare propylbenzene by acylation followed by reduction.

Synthesis

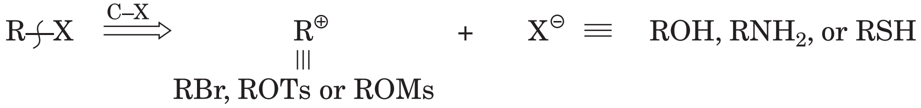


3.1.4 One-Group C–X Disconnections

In ethers, amides and sulphides, the position of disconnection can easily be decided and it is the bond joining the carbon to the heteroatom (X). This basic approach to synthetic designing is called 'one-group C—X disconenction' because we have to recognize only one functional group to know that we can make the disconnection. The label C—X, C—N, C—O, etc., can be used on the retrosynthetic arrow.

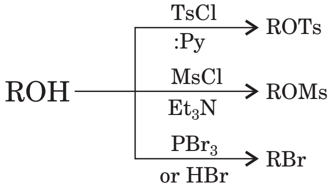
Since carbon is less electronegative than the heteroatom X, disconnection through the C—X bond will give a cationic carbon synthon. The synthetic equivalent or reagent for it will usually have a good leaving group attached to R. The reagents for anionic synthons are alcohols (ROH), amines (RNH_2) or thiols (RSH). The corresponding reactions are therefore nucleophilic substitutions of some kind and the reagents will be alkyl halides, tosylates, mesylates, etc.

Retrosynthetic analysis of alcohols, ethers, alkyl halides and sulphides



$$R\text{—}X \xRightarrow{C\text{–}X} \underset{\text{RBr, ROTs or ROMs}}{\underset{|||}{R^{\oplus}}} + X^{\ominus} \equiv \text{ROH, RNH}_2\text{, or RSH}$$

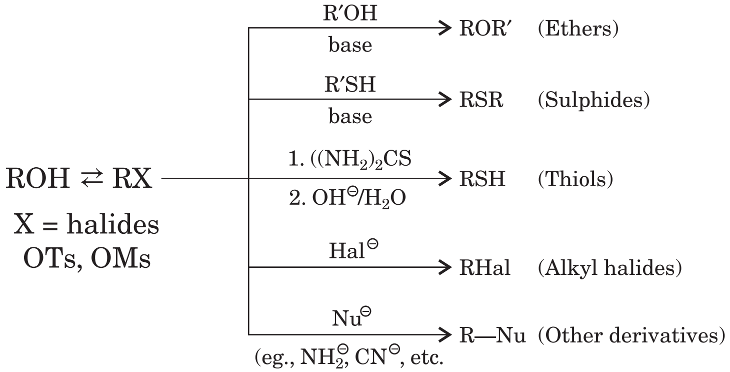
Alkyl halides, tosylates and mesylates can be made from alcohols and as alcohols can be made by C—C bond formation, they must be treated as the central functional group.



Synthesis of alcohols, ether, alkyl halides and sulphides

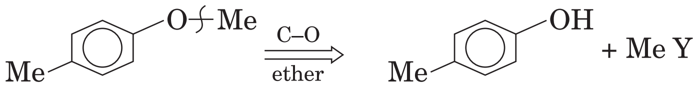
$$\text{RBr, ROTs or ROMs} + \text{OH}^{\ominus} \text{ or } \text{H}_2\text{O, R}'\text{OH, NaX, or R}'\text{SH} \longrightarrow \text{ROH, ROR}', \text{RX or RSR}'$$

Aliphatic compounds derived from alcohols:



Examples of some syntheses involving one group 'C—X disconnection':

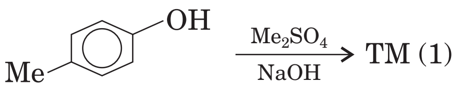
1. *Retrosynthetic analysis*



TM (1)

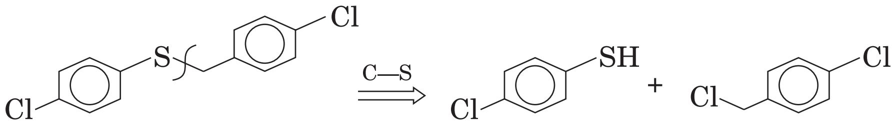
The disconnection is easy because the ether has a reactive side (Me, by S_N2) and an unreactive side (ring carbon).

Synthesis



2. Chlorobenside (an acaricide that kills mites and ticks) can be synthesized by a Williamson type synthesis and so disconnection is to be done on the alkyl not on the aryl side. Ignoring to write the unsuitable pair of synthons from an alternative disconnection, the viable retrosynthetic analysis is presented below.

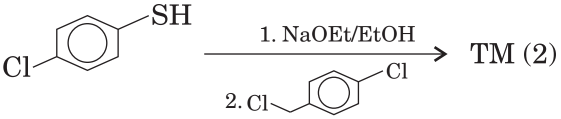
   Retrosynthetic analysis



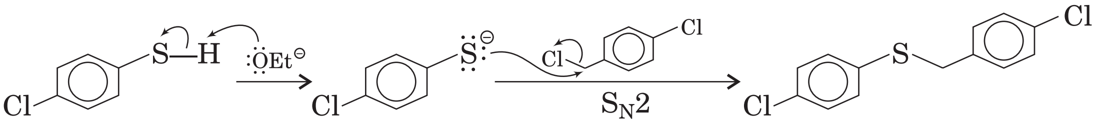
Chlorbenside
TM (2)

Synthetic equivalents

Synthesis

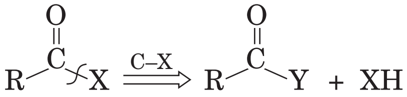


Mechanism



Retrosynthetic analysis of carboxylic acid derivatives

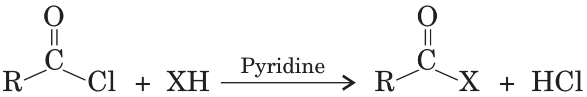
Carboxylic acid derivatives are easy to disconnect since we always choose the bond between the carbonyl group and the heteroatom for our first disconnection.



$$R-\overset{\overset{O}{\|}}{C}-X \xRightarrow{C-X} R-\overset{\overset{O}{\|}}{C}-Y + XH$$

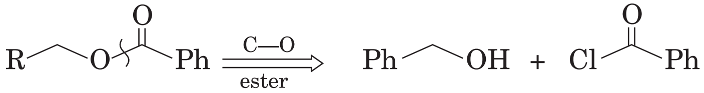
Synthesis of carboxylic acid derivatives

The synthesis can be carried out in several ways, e.g., using acid chlorides, acid anhydrides, etc. Acid chlorides are frequently used as a reagent because they are the most reactive out of all acid derivatives and can be easily synthesized from the acid themselves and $SOCl_2$ or PCl_5.



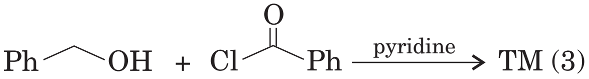
$$R-\overset{\overset{O}{\|}}{C}-Cl + XH \xrightarrow{\text{Pyridine}} R-\overset{\overset{O}{\|}}{C}-X + HCl$$

3. *Retrosynthetic analysis*

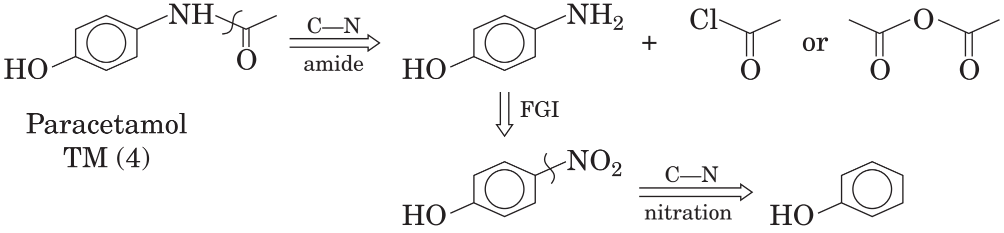


Benzyl benzoate
TM (3)

Synthesis

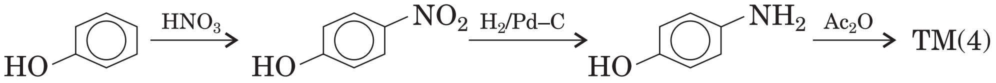


4. *Retrosynthetic analysis*



Paracetamol
TM (4)

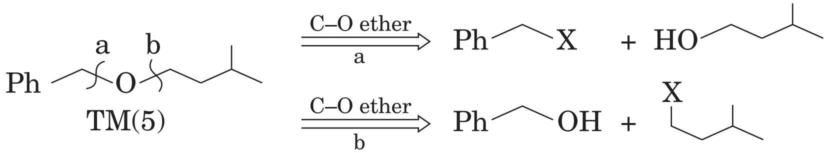
Synthesis



Phenol

(the *ortho*-isomer
in separated by
steam distillation)

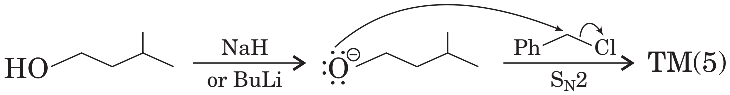
5. *Retrosynthetic analysis*



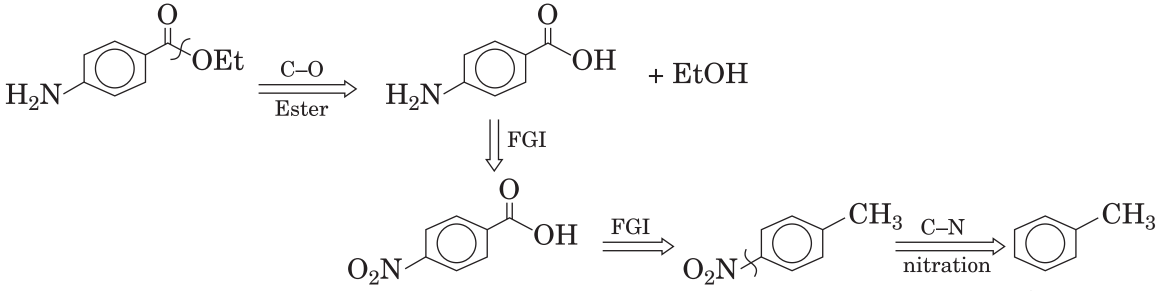
TM(5)

The benzyl halide (disconnection 'a') is more S_N2 reactive (because of conjugated and hence, more stable T.S.) compared to isopentyl halide. However, the deciding point in favour of route (a) is that route (b) might well lead to elimination.

Synthesis

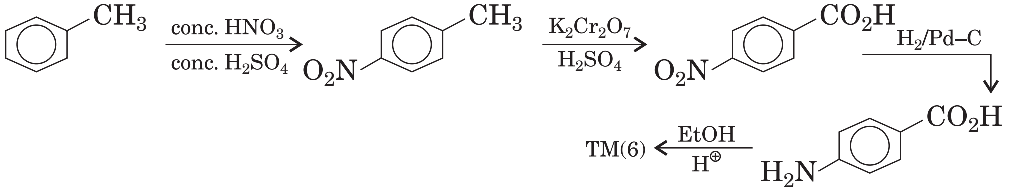


6. *Retrosynthetic analysis*

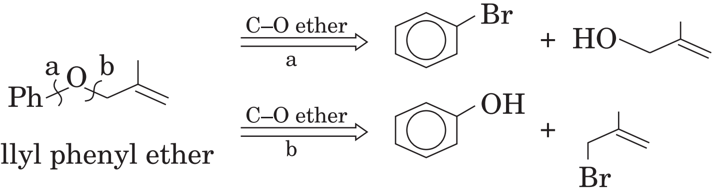


Toluene

Synthesis



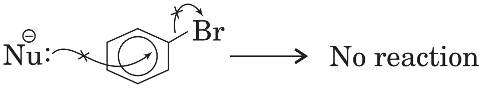
7. *Retrosynthetic analysis*



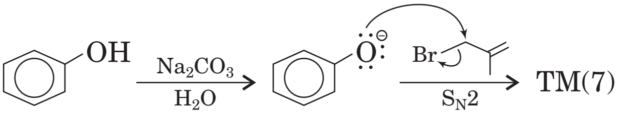
An allyl phenyl ether

TM(7)

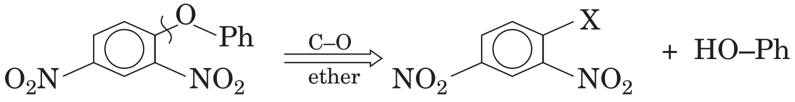
The pathway involving the disconnection (a) is not normally possible (except through benzyne), since S_N2 reaction at an sp^2 carbon in bromobenzene does not take place. The pathway involving the disconnection (b) is viable, since the phenoxide ion can readily displace Br from the allylic bromide by an S_N2 reaction.



Synthesis



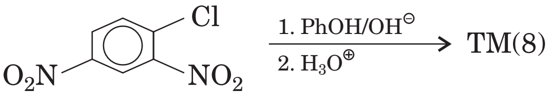
8. *Retrosynthetic analysis*



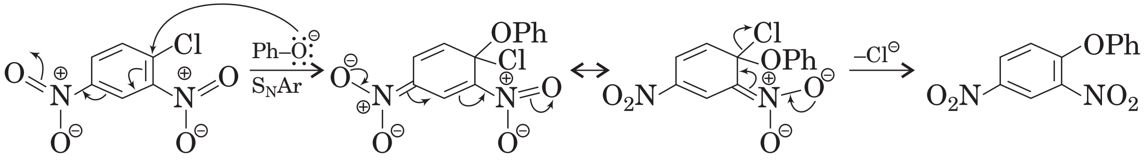
TM (8)

The ether is disconnected on the dinitrophenyl side because the reverse is an activated nucleophilic aromatic substitution (S_NAr) which occurs smoothly.

Synthesis



Mechanism:



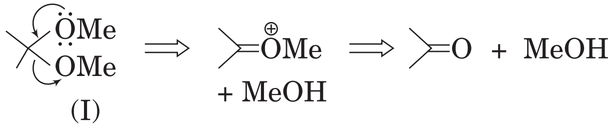
3.1.5 Two-Group C—X Disconnections

The disconnections in which we use one functional group to help disconnect another elsewhere in the molecule are known as two-group disconnections. It is better to use two-group disconnections because they are more efficient than one-group disconnections. These disconnections can be explained under the following headings:

(a) 1,1-Disconnections

Let us consider the disconnection of 1,1-difunctionalised compounds like acetals, cyanohydrines, etc.

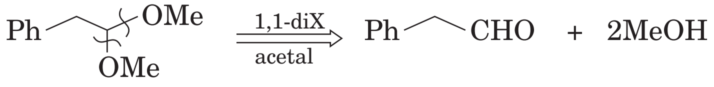
Acetals: In these compounds (I), we can use one oxygen atom to help disconnect the other as shown below:



(I)

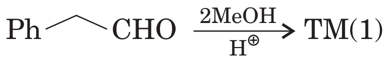
Both C—O bonds have been disconnected and the operation can be labelled as '1,1-diX' to indicate that it is a two-group (diX) disconnection. That both the functional groups are attached to the same carbon atom is indicated by the numbers '1,1'. Let us take the example of retrosynthetic analysis of acetal (1) involving two-group disconnection.

Retrosynthetic analysis

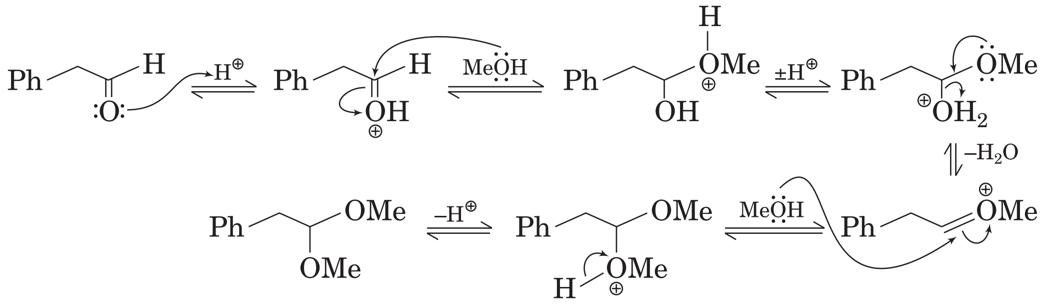


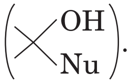
TM(1)

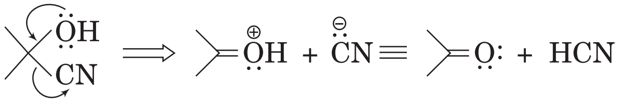
Synthesis



Mechanism:



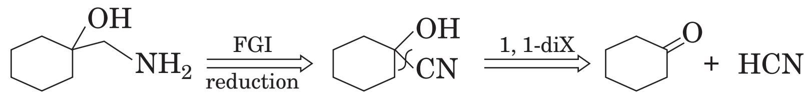
Cyanohydrines: If one heteroatom is present as an —OH group, then only one nucleophile so involved . Molecules such as cyanohydrines (II) are obviously made from carbonyl compounds and HCN



(II)

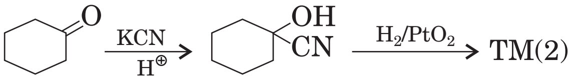
Let us consider the retrosynthetic analysis of the hydroxy amine (2).

Retrosynthetic analysis



TM(2)

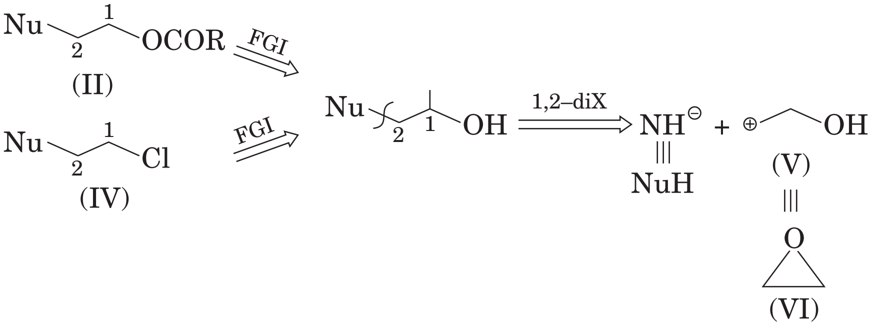
Synthesis



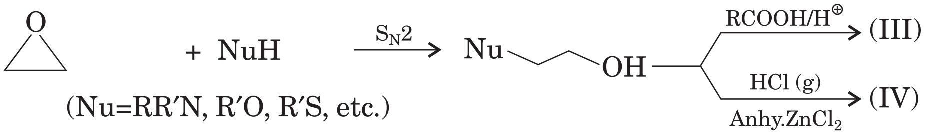
(b) 1,2-Disconnections

Alcohols: Compounds with heteroatoms on adjacent carbon atoms, e.g., (III) and (IV), are most helpfully considered as derivatives of alcohols. Disconnection gives the synthon (V), the reagent for which is the epoxide (VI).

Retrosynthetic analysis

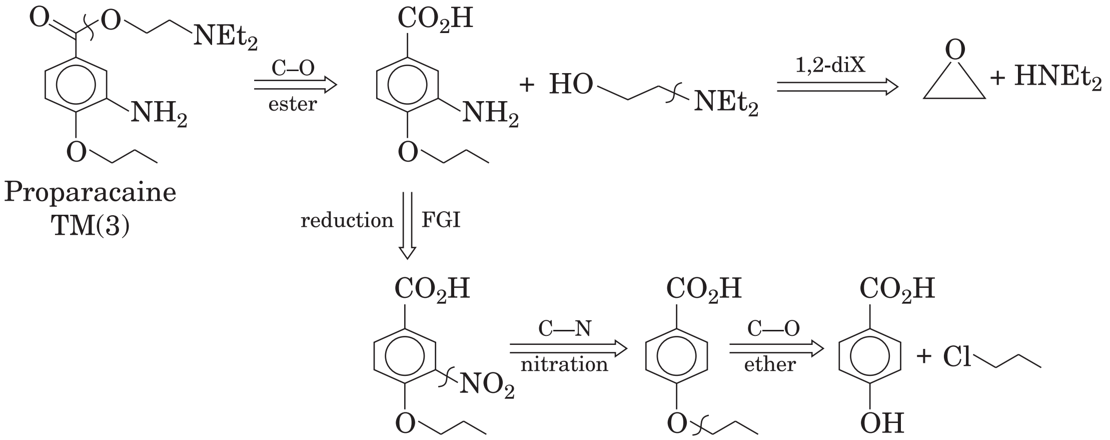


Synthesis



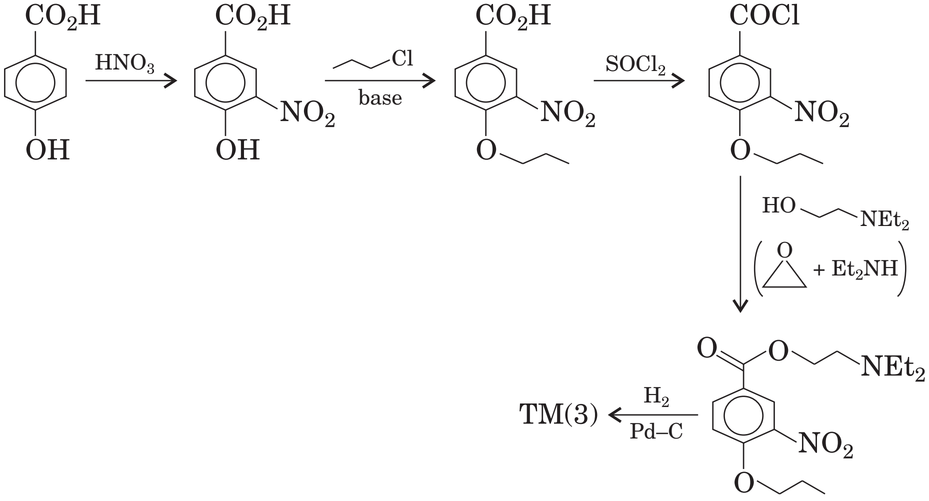
Example:

Retrosynthetic analysis

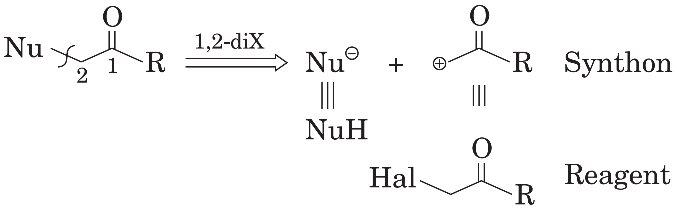


Proparacaine
TM(3)

Synthesis

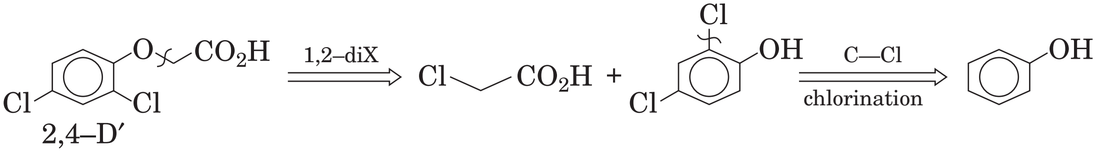


Carbonyl compounds If in a difunctionalised compounds, one of the functional group is a carbonyl group, then disconnection of the C—Nu bond gives the electrophilic synthon α-carbonyl cation (a very unstable species) and the best synthetic equivalents or reagents for these synthones are α-halo carbonyl compounds.



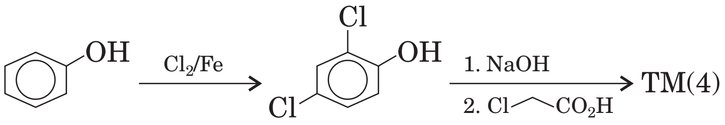
This disconnection to this cationic synthon is a case of two-group disconnection because the α-halo carbonyl equivalents can be easily prepared by halogenation of ketones, esters or carboxylic acids and the carbonyl group adjacent to the halogen atom makes them extremely reactive electrophiles. For example, the herbicide '2,4-D' can obviously be disconnected by this approach.

Retrosynthetic analysis



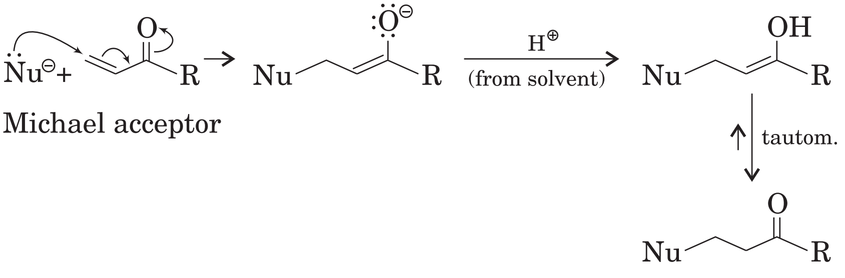
2,4–D′
TM(4)

Synthesis



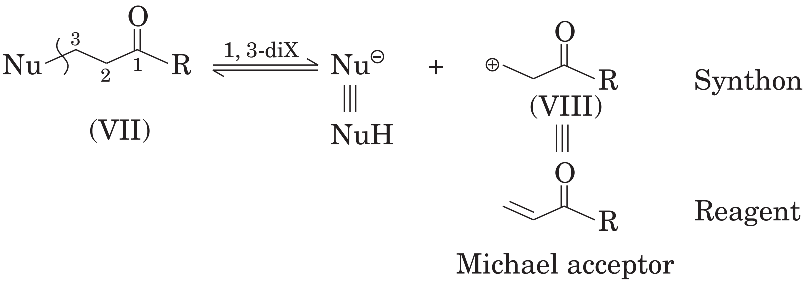
(c) 1,3-Disconnections

α, β-unsaturated carbonyl compounds undergo Michael addition reaction as shown below:



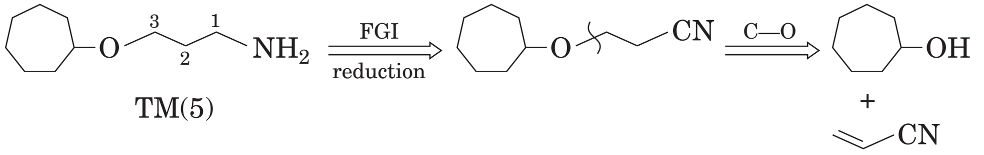
(VII)

The ketones (VII) can, therefore, be disconnected as 1,3-diX compound because they correspond to this forward reaction. These Michael acceptors have an electrophilic site two atoms away from the carbonyl group, and are, therefore, the synthetic equivalents corresponding to the synthons (VIII).



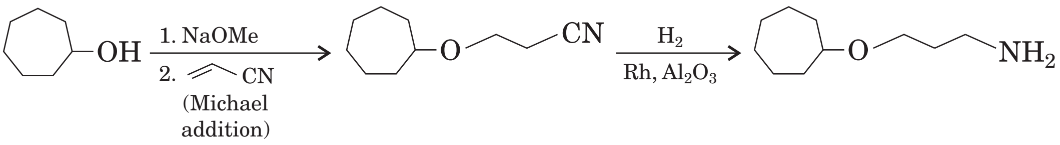
Examples

1. *Retrosynthetic analysis*

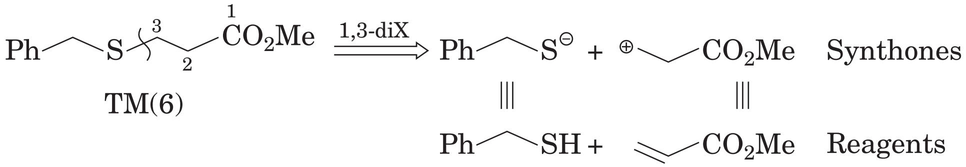


TM(5)

Synthesis

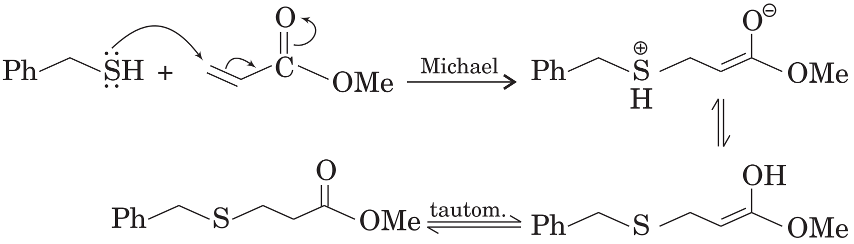


2. *Retrosynthetic analysis*



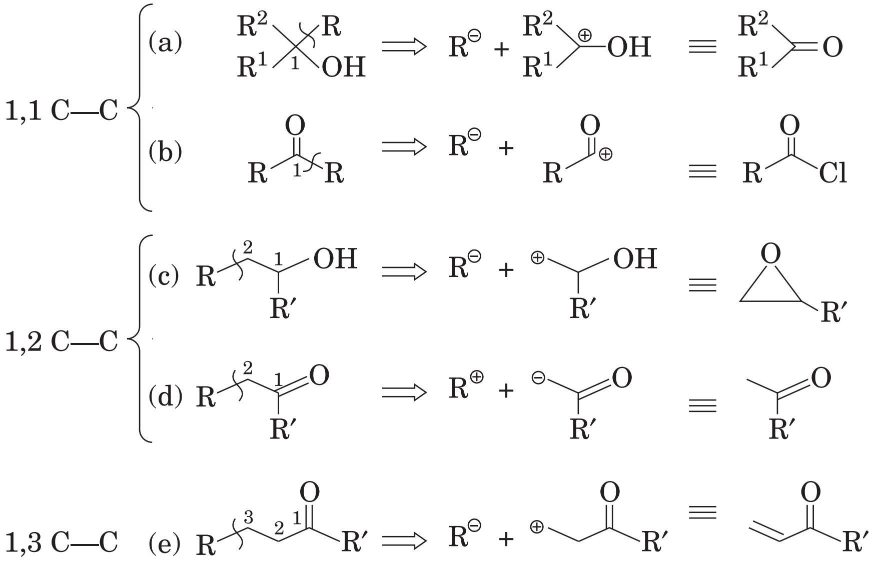
TM(6)

Synthesis



3.1.6 One-Group C—C Disconnections

The C—C bond forming reactions are probably the most important reactions in organic synthesis. C—C disconnections are, therefore, very much important in retrosynthetic analysis. These are, in fact, more challenging than C—X disconnection (where there is only one choice of disconnection) because organic molecules contain may C—C bonds and we must learn which one is to be disconnected. In one way they are easier than C—X disconnections because reagents are available for both electrophilic (e.g., RX, R-OTs, R—OMs, etc.) and nuclophilic (e.g., RMgX, RLi, etc.) carbon, whereas heteroatoms are almost always added as nucleophiles. One-group C—C disconnections are summarized as follows:



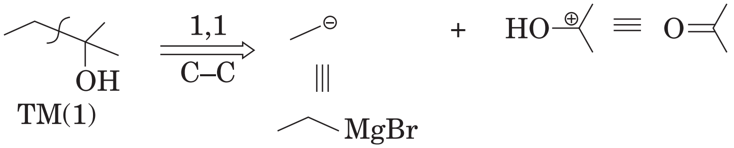
C—C disconnections involving only one functional group are known as one-group C—C disconnections. All of the one-group C—C disconnections (a), (b), (c) and (e) require reagents for the carbanion synthon $R^{\ominus}$. Simple carbanions are almost never formed in reactions, so reagents in which carbon is joined to more electropositive atom such as metal is required. The most important reagents are alkyl lithiums (RLi) and Grignard reagents (RMgX).

One-group C—C disconnections can further be divided into three sections: (1) 1,1 C—C disconnections, (2) 1,2 C—C disconnections and (3) 1,3 C—C disconnections.

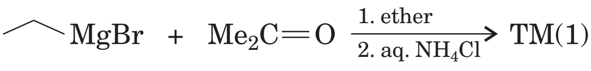
1. 1,1 C—C disconnections: Disconnections in which the bond being disconnected is attached to the same C atom as the functional group are designated as 1,1 C—C disconnections. For example:

(a) Synthesis of alcohols: Any alcohol can be disconnected at the C—C bond next to oxygen [the disconnection (a)] to give an aldehyde or a ketone and a Grignard reagent as starting materials. The synthesis of the alcohol (1), for example, may be designed as follows:

Retrosynthetic analysis



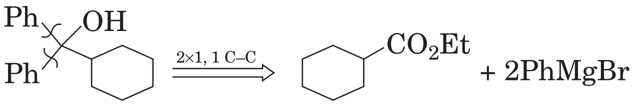
Synthesis



$$\text{CH}_3\text{CH}_2\text{MgBr} + \text{Me}_2\text{C}{=}\text{O} \xrightarrow[\text{2. aq. NH}_4\text{Cl}]{\text{1. ether}} \text{TM(1)}$$

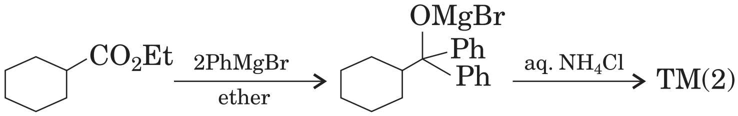
When an alcohol contains two identical R groups, an alternative approach is to disconnect both of them at once and in that case, the starting material is an ester. This type of disconnections are called *double disconnections*. In such a reaction, one molecule of RMgX displaces EtO$^{\ominus}$ from the ester to yield a ketone. Being more reactive than the ester it reacts readily with a second molecule of Grignard reagent. The synthesis of the alcohol (2), for example, may be designed as follows:

Retrosynthetic analysis

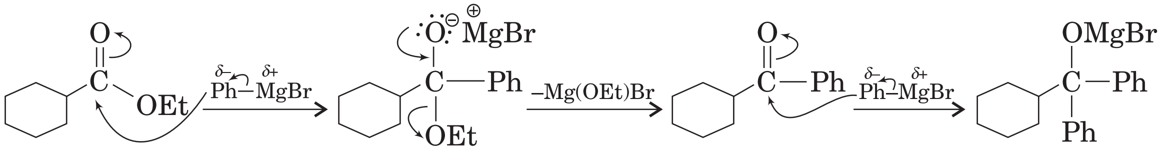


TM(2)

Synthesis

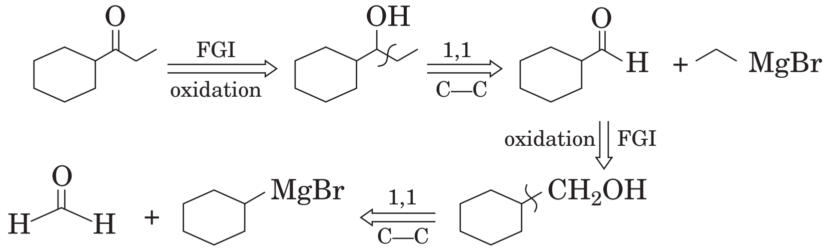


Mechanism:

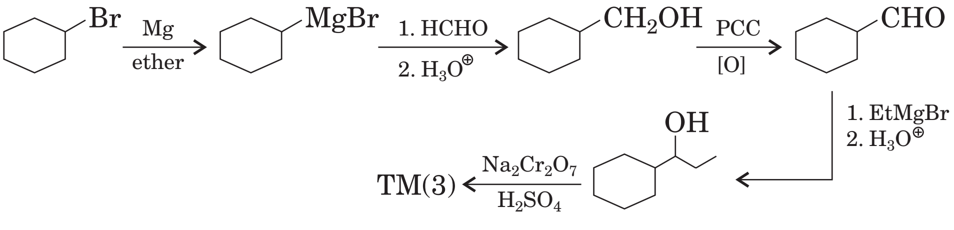


Synthesis of aldehydes and ketones from alcohols: The easiest way to synthesize aldehydes and ketones *via* this disconnection is by oxidation of the corresponding alcohol. For example, the synthesis of the ketone (3) can be designed as follows:

Retrosynthetic analysis



Synthesis

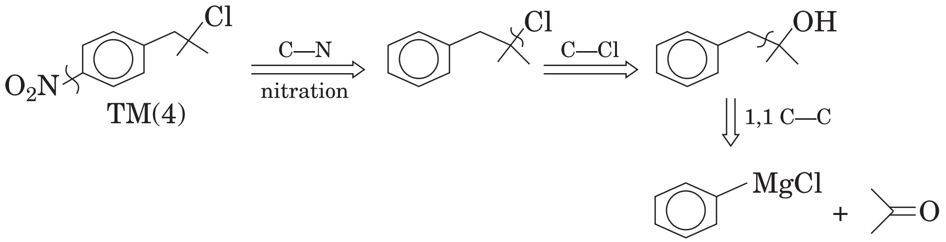


Pyridinium chlorochromate (PCC), $\overset{\oplus}{\text{Py}}\text{H}\ \text{CrO}_3\text{Cl}^{\ominus}$, (a complex of chromium trioxide with pyridine and HCl) is a better reagent for limited oxidation of primary alcohols to aldehydes.

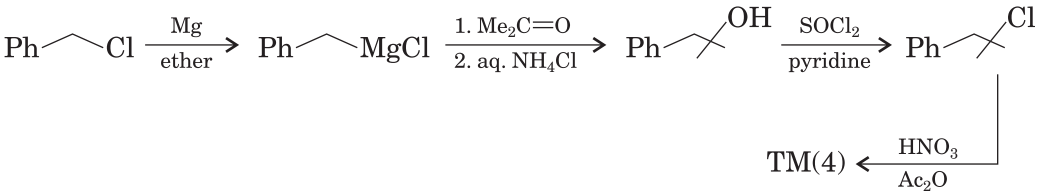
Pyridinium dichloromate (PDC), $2\overset{\oplus}{\text{Py}}\text{H}\,\text{Cr}_2\text{O}_7^{2-}$, may also be used in CH_2Cl_2 solution.

Synthesis of other compounds from alcohols: Most of the C—X disconnections lead back to alcohols as starting materials. So complete synthesis of a large number of compounds are now possible. For example, the synthesis of the alkyl chloride (4) can be designed as follows:

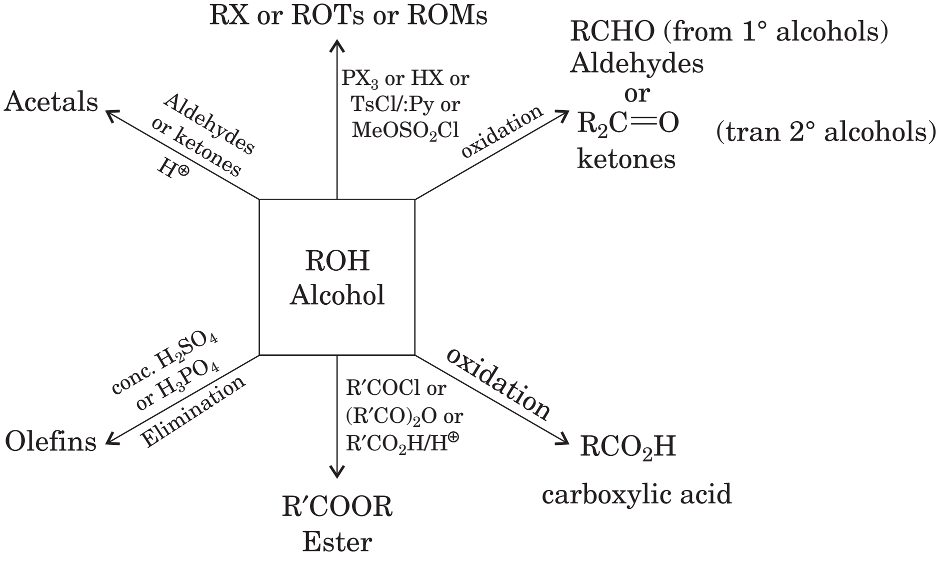
Retrosynthetic analysis



Synthesis

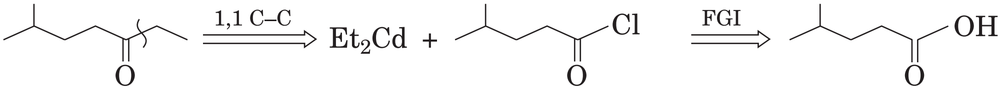


Alcohols are the key starting materials in synthesis because they can be converted into a whole family of other mono-functionalised compounds. Also, they can be synthesized readily from carbonyl compounds and esters by a Grignard reaction.



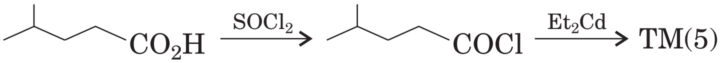
(b) Synthesis of carbonyl compounds: 1,1 C—C disconnection of ketones gives two synthons namely an acyl cation and a carbanion [the disconnection (b)]. The synthetic equivalents or reagents for these synthons are an ester or an acid chloride and an organometallic compound, respectively. Esters should not be used because the resulting ketone is relatively more reactive than ester towards the organometallic reagent and further reaction leads to the formation of an alcohol. Therefore, an acid chloride should be used instead of an ester and less reactive organocadmium compound, which can react with an acid chloride but not with an ester, should be used instead of Grignard reagent. This strategy has been used in the synthesis of the ketone (5).

Retrosynthetic analysis



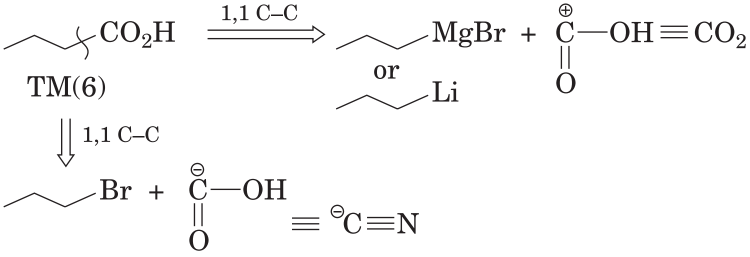
TM(5)

Synthesis

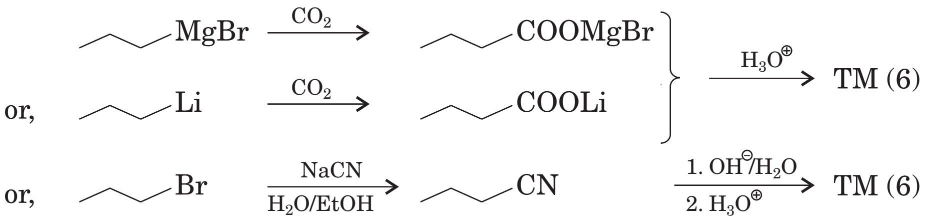


(c) Synthesis of carboxylic acids: Direct disconnection is possible at this oxidation level since CO_2 reacts with Grignard reagents or alkyl lithium to yield a carboxylic acid. This method complements hydrolysis of cyanides since the disconnection is the same but the polarity is different. The synthesis of the carboxylic acid (6), for example, can be designed as follows:

Retrosynthetic analysis



Synthesis

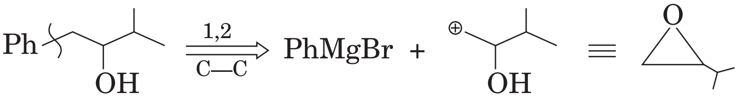


It is to be noted that the *tert*-alkyl acid (e.g., Me_3CCOOH) could not be prepared by the cyanide method and this in because the S_N2 displacement at the tertiary centre is not possible due to steric hindrance.

2. 1,2 C—C disconnections: Disconnections in which the bond being disconnected in two atoms away from the functional group are designated as 1,2 C—C disconnections.

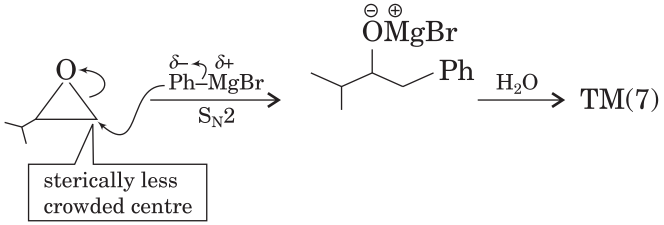
(a) Synthesis of alcohols: 1,2 C—C disconnection of an alcohol [the disconnection (c)] gives two synthons namely a β-hydroxy-carbocation and a carbanion ($R^{\ominus}$) whose synthetic equivalents are an epoxide and an organometallic compound, respectively. The synthesis of the alcohol (7), for example, can be designed as follows:

Retrosynthetic analysis



TM (7)

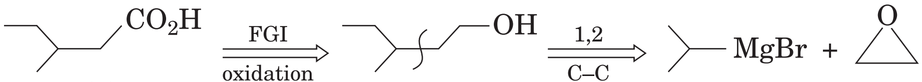
Synthesis



sterically less crowded centre

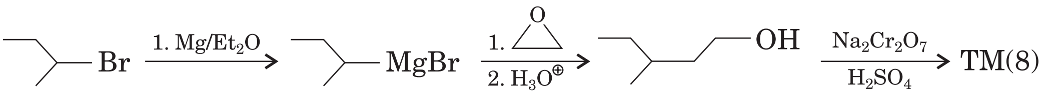
Synthesis of carboxylic acids from alcohols Carbonyl compounds can be derived from alcohols by oxidation, so the above disconnection applied for the synthesis of alcohols can also be used for carboxylic acids. For example, the synthesis of the acid(8) can be designed as follows.

Retrosynthetic analysis

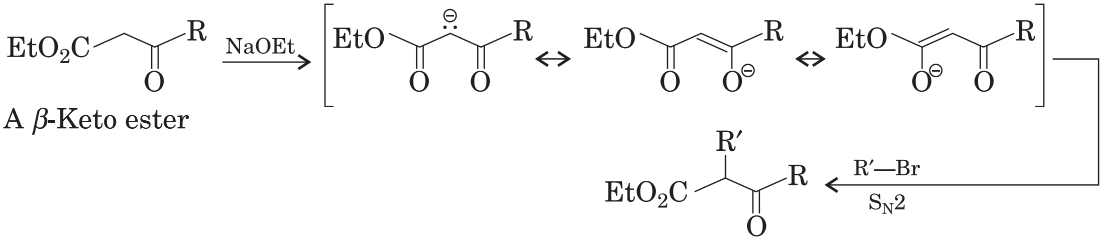


TM(8)

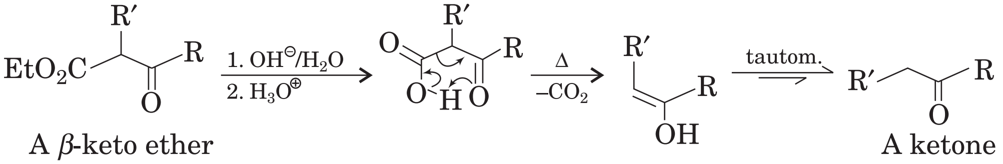
Synthesis



(b) Synthesis of carbonyl compounds: The 1,2 C—C disconnection of carbonyl compounds [the disconnection (d)] requires the alkylation of an enol or enolate anion by an alkyl halide. However, there are some problems in its execution. The product may also undergo alkylation and the enolate ion may prefer to react with the starting and the product ketones rather than the alkyl halide. For successful alkylation to take place, an activating group like CO_2Et must be present on the α-carbon. The alkylation then takes place as follows:

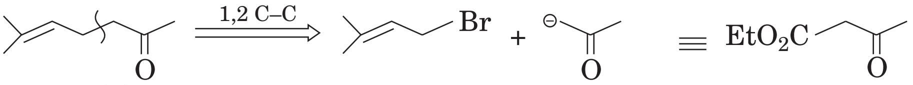


The activating —CO$_2$Et group stabilizes the enolate anion by conjugation and for this reason, the keto ester becomes almost completely converted into the enolate anion by the base. The enolate anion does not react with the keto ester, partly because the enolate anion is much more stable than that in which the activating —CO$_2$Et group is absent and partly because no keto ester is left. The alkyl halide is added in a separate step so that no base remains to form an anion of the product. The activating group, which enhances the reaction in one direction, must be easily removed once the reaction is over. When the alkylation product of the β-keto ester is hydrolyzed and the resulting carboxylic acid is decarboxylated on heating, the —CO$_2$Et group is removed to give a ketone.



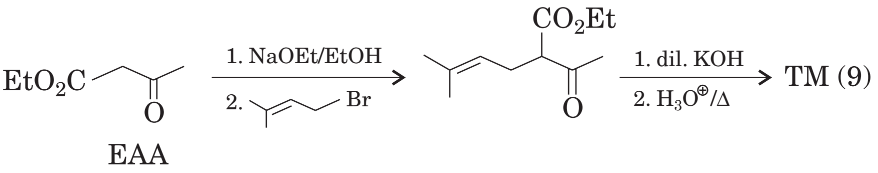
The synthesis of the unsaturated ketone (9), for example, can be designed as follows:

Retrosynthetic analysis



TM(9)
An industrial
precursor to β-carotene

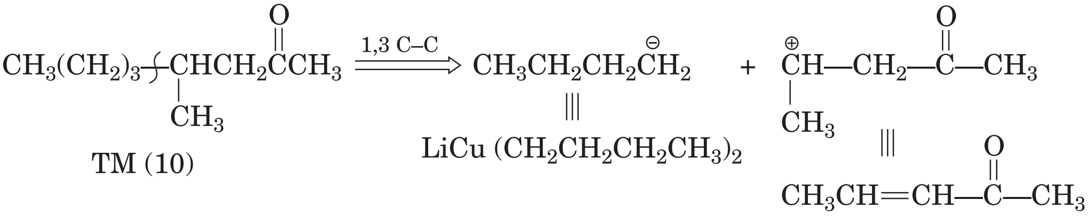
Synthesis



3. 1,3 C—C disconnections: Disconnections in which the bond being disconnected, i.e., the strategic bond, is three atoms away from the functional group are termed as 1,3 C—C disconnections.

Synthesis of carbonyl compounds: 1,3 C—C disconnection of ketones gives two synthons namely a carbanion and a *β*-ketocarbocation whose synthetic equivalents are a Grignard reagent or RLi and an *α,β*-unsaturated carbonyl compound. This synthesis involves the Michael addition of carbanions to *α,β*-unsaturated carbonyl compounds. The synthesis of the ketone (10) and (11), for example, can be designed as follows:

Retrosynthetic analysis



$$CH_3(CH_2)_3 \not{-} \underset{\displaystyle CH_3}{CH}CH_2\overset{\displaystyle O}{\overset{\|}{C}}CH_3 \xRightarrow{1,3\ C\text{–}C} CH_3CH_2CH_2\overset{\ominus}{C}H_2 + \underset{\displaystyle CH_3}{\overset{\oplus}{C}H}\text{—}CH_2\text{—}\overset{\displaystyle O}{\overset{\|}{C}}\text{—}CH_3$$

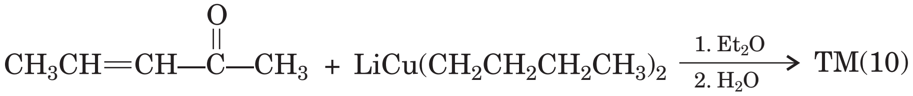
$$CH_3CH_2CH_2\overset{\ominus}{C}H_2 \equiv LiCu\,(CH_2CH_2CH_2CH_3)_2$$

$$\overset{\oplus}{C}H(CH_3)\text{—}CH_2\text{—}\overset{\displaystyle O}{\overset{\|}{C}}\text{—}CH_3 \equiv CH_3CH{=}CH\text{—}\overset{\displaystyle O}{\overset{\|}{C}}\text{—}CH_3$$

TM (10)

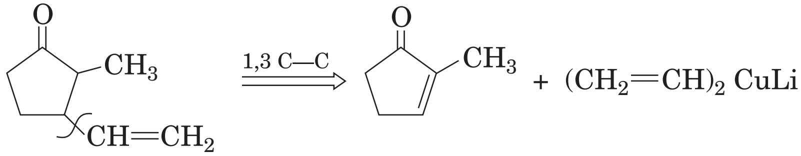
An *α*, *β*-unsaturated ketone

Synthesis



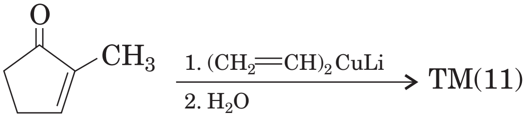
$$CH_3CH{=}CH\text{—}\overset{\displaystyle O}{\overset{\|}{C}}\text{—}CH_3 + LiCu(CH_2CH_2CH_2CH_3)_2 \xrightarrow[2.\ H_2O]{1.\ Et_2O} TM(10)$$

Retrosynthetic analysis

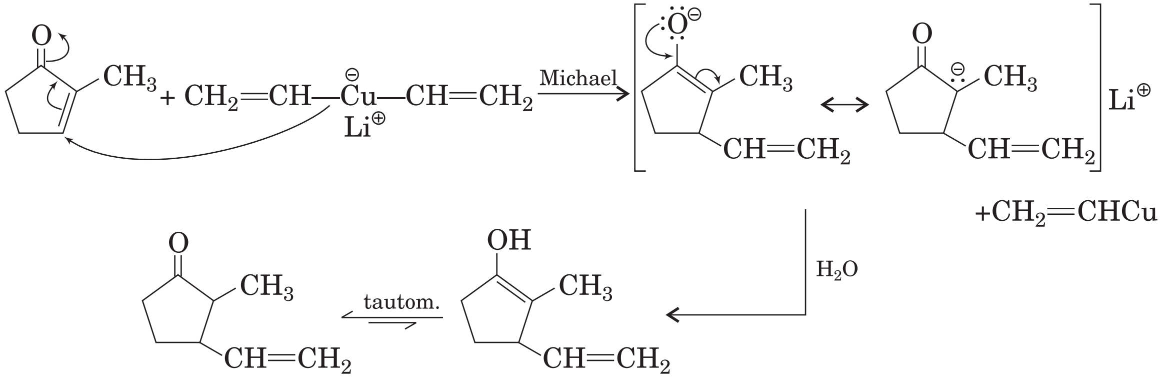


TM (11)

Synthesis



Mechanism:

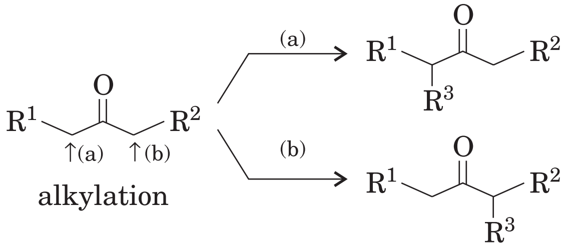


3.1.7 The Problem of Regioselectivity and Its Solution in Alkylation of Ketone and in Michael Addition

A reaction is said to be regioselective when one of the several possible constitutional isomers is formed predominantly. For example, Markownikoff's addition, Saytzeff and Hofmann elimination are regioselective reactions. A regioselective problem is how to react one specific part of a single functional group and no other.

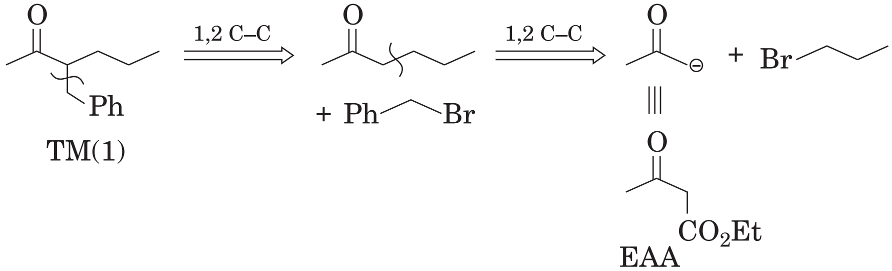
3.1.7.1 Alkylation of Ketones

How can one side of an unsymmetrical ketone be alkylated is a regioselective problem.



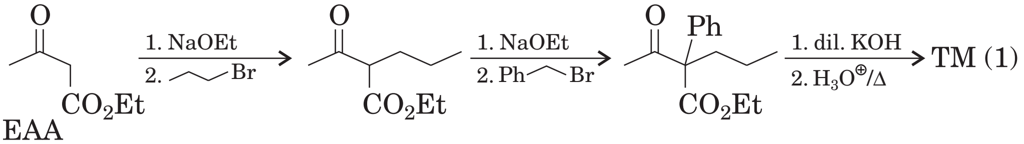
The synthesis of the ketone (1), for example, can be designed as follow:

Retrosynthetic analysis



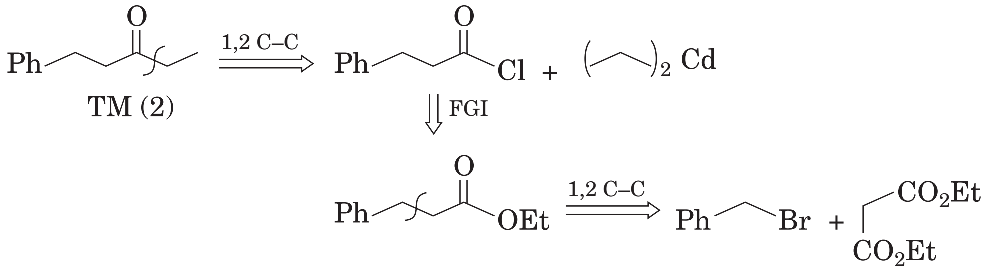
An activating group must be introduced for alkylation to be done at a particular position. Thus, the starting material must be the synthetic equivalent for acetone enolate ion and it is ethyl acetoacetate.

Synthesis

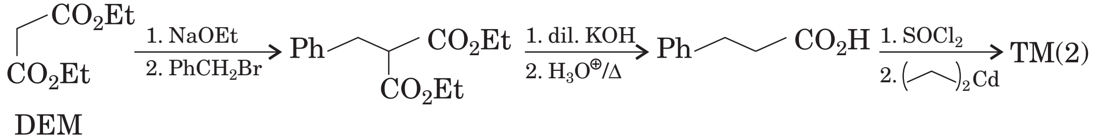


Due to introduction of the —CO_2Et group, the regioselective problem disappears and this is because EAA (a reactive methylene compound) enolise on one side only. Therefore, unsymmetrical ketones can be prepared by alkylation of β-keto esters. Diethyl malonate can also be used for this purpose. For example, the synthesis of the ketone (2) can be designed as follows:

Retrosynthetic analysis

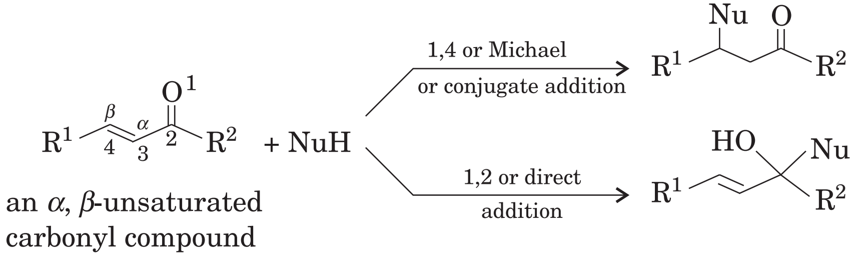


Synthesis



3.1.7.2 *Michael addition*

It is a nucleophilic addition reaction of α,β-unsaturated carbonyl compounds. Two constitutional isomers can be formed by 1,2- and 1,4-addition. The problem of direct (1,2) versus Michael (1,4) addition to α,β-unsaturated carbonyl compounds can be solved without finding another strategy.



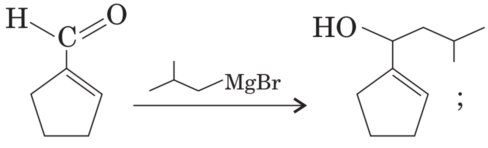
The Michael addition can be favoured if we follow the general mechanistic principles:

(i) The Michael addition product is thermodynamically favoured since the more stable C═O bond remains intact and the weaker C═C bond is destroyed.

(ii) Direct addition is more easily reversed than Michael addition. Therefore, the more the nucleophile is stable or the more the direct addition is reversible, the more the Michael addition is favoured.

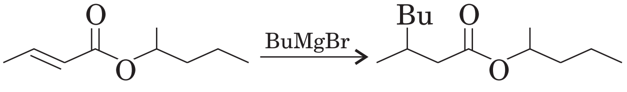
(iii) Hard acids prefer hard bases and soft acid prefer soft bases. Since the carbonyl carbon is the harder site and the β-carbon atom is the softer site, strongly basic nucleophiles (hard bases) tend to attack directly (hard–hard interaction), whereas weakly basic nucleophiles (soft bases) tend to attack in Michael fashion (soft–soft interaction).

Direct addition is most likely with unsaturated aldehydes and acid chlorides, whereas Michael addition is most likely with ketones and esters. Hence, Grignard reagents add directly to the aldehyde (3) and in Michael fashion to the ester (4).



TM (3)

;



TM (4)

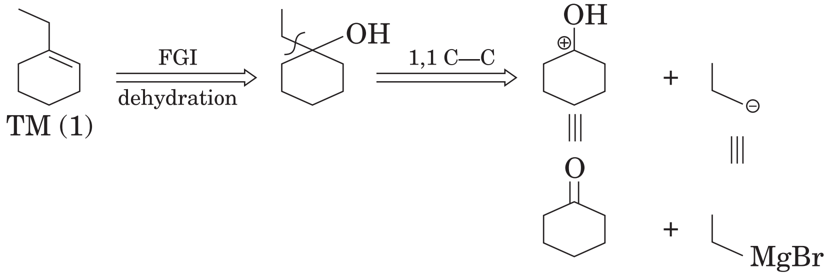
Nucleophiles like RLi, $NH_2^{\ominus}$, $RO^{\ominus}$ and hydride reducing agents are more likely to add direct (i.e., 1,2), whereas RMgBr, neutral amines, $RS^{\ominus}$ and stable carbanions [e.g., $CH_3CO\overset{\ominus}{C}HCO_2Et$, $\overset{\ominus}{C}H(CO_2Et)_2$ etc.] are more likely to add in Michael fashion.

3.1.8 Synthesis of Alkenes

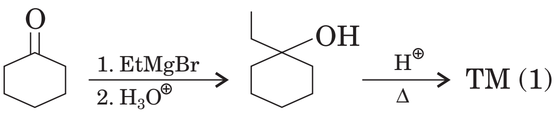
Alkenes (olefins) can be synthesized: (i) by dehydration of alcohols, (ii) by elimination of HX from alkyl halide and (iii) by the Wittig reaction.

(i) **Dehydration of alcohols:** It is carried out under acidic conditions. Acids must be fairly strong and must have a non-nucleophilic counter ion otherwise substitution may take place. The common reagents are $KHSO_4$ (crystalline solid and easier to handle than sulphuric acid), Al_2O_3, phosphoric acid and $POCl_3$ in pyridine. This route is particularly good for cyclic or branched olefins. A double-bond inside a six-membered ring is greatly preferred to one outside, and the *cis*-isomer is possible. For example, the syntheses of the alkene (1) and (2) can be designed as follows:

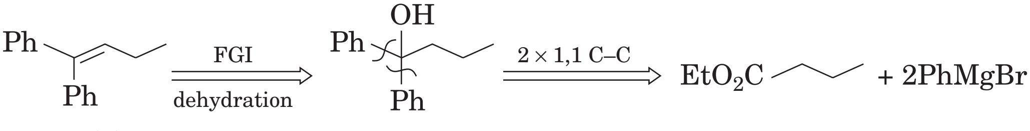
Retrosynthetic analysis



Synthesis



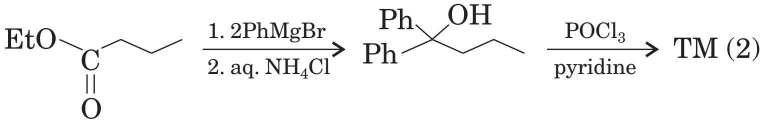
Retrosynthetic analysis



TM (2)

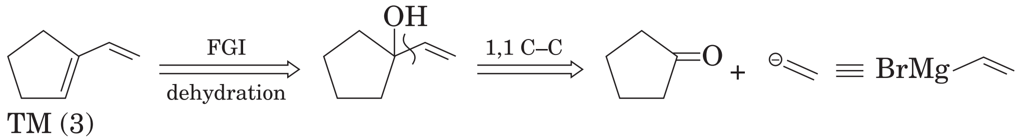
Putting OH at the branch point is a better strategy as disconnection of the alcohol then gives starting materials.

Synthesis

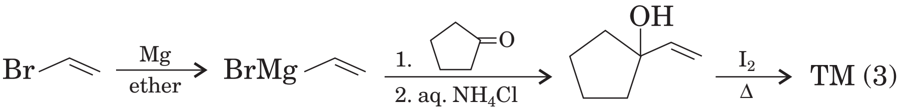


Dienes can be made by this approach if vinyl Grignards are used and this is because the vinyl group blocks dehydration in one direction and makes the reaction faster by the E1 mechanism as the intermediate is a resonance stabilized allylic cation. This synthesis of the diene (3), for example, can be designed as follows:

Retrosynthetic analysis

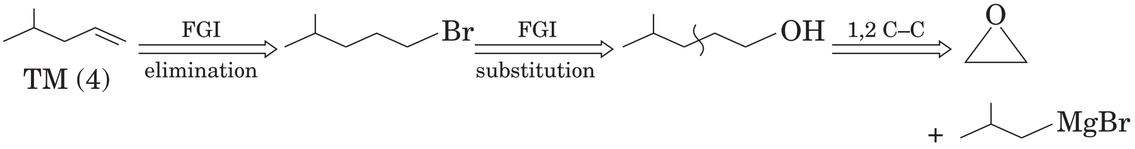


Synthesis

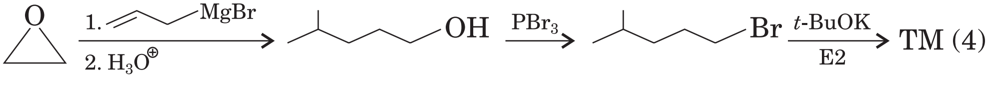


(ii) **Elimination of HX from RCH$_2$X:** Elimination of HX from alkyl halides follow the same strategy, as the halide is usually made from an alcohol. The synthesis of the alkene (4), for example, can be designed as follows:

Retrosynthetic analysis



Synthesis



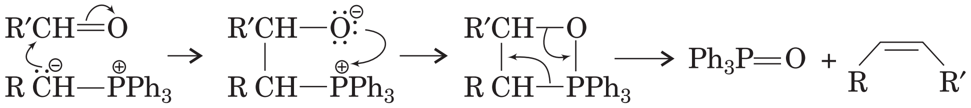
(iii) **Wittig reaction:** The reaction of an aldehyde (RCHO) or a ketone (R$_2$C=O) with phosphorus ylide (the Wittig reagent) to yield an alkene is known as the *Wittig reaction*. This can be prepared as follows:

$$\mathrm{RCH_2Br} \xrightarrow[\mathrm{S_N2}]{:\mathrm{PPh_3}} \mathrm{Ph_3}\overset{\oplus}{\mathrm{P}}\text{—}\mathrm{CH_2R}\ \mathrm{Br}^{\ominus} \xrightarrow[\text{base}]{\text{BuLi}} \mathrm{Ph_3}\overset{\oplus}{\mathrm{P}}\text{—}\overset{\ominus}{\ddot{\mathrm{C}}}\mathrm{H_2}$$

Ylide
(the Wittig reagent)

The starting halide should be primary because the initial reaction is an S_N2 one.

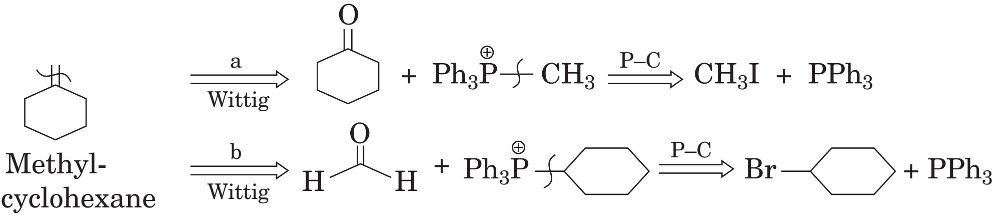
The Wittig reaction proceeds through the steps as follows:



The Wittig reaction forms both σ and π bonds in one reaction so the disconnection is at the C═C with a nearly free choice of which end comes from the alkyl halide and which from the carbonyl compound.

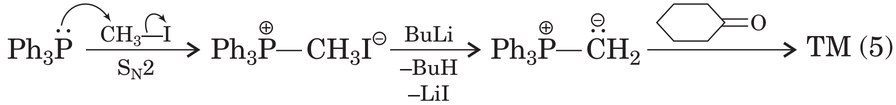
The exo-alkene (5), which is not possible to synthesize by elimination (because of less thermodynamic stability), can easily be synthesized by either of the Wittig routes. However, the route (a) is much easier than the route (b) because S_N2 attack by Ph_3P on methyl halide is sterically much favourable than S_N2 attack on cyclohexyl halide (a 2° halide). Also, cyclohexanone is easier to handle than formaldehyde.

Retrosynthetic analysis



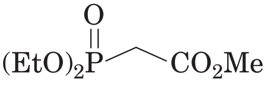
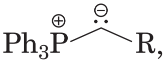
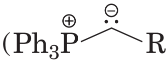
Methyl-
enecyclohexane
TM (5)

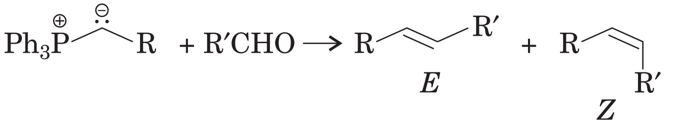
Synthesis

Route (a): 

Some relevant topics

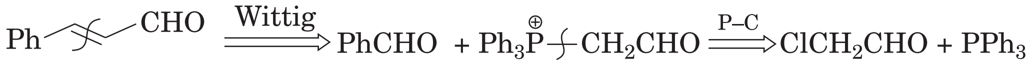
1. Stereoselectivity in Wittig reactions

In Wittig reactions, stabilized ylides [from  or , where R═Ar, COR, C═C, etc.] react with aldehydes to give mainly *E*. alkenes while unstabilized yields (, R = alkyl) give mainly *Z* alkenes.



The synthesis of the *E* α, β-unsaturated aldehyde (6), for example, can be designed as follows:

Retrosynthetic analysis



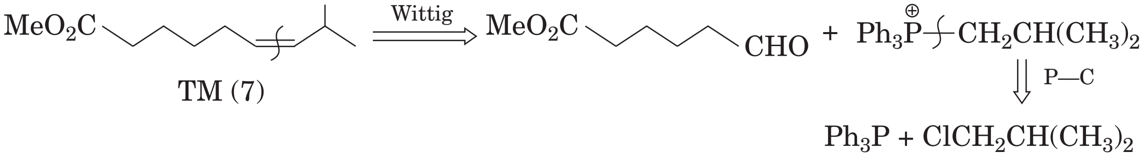
TM (6)

Synthesis

$$Ph_3P \xrightarrow{ClCH_2CHO} Ph_3\overset{\oplus}{P}—CH_2CHO\ Cl^{\ominus} \xrightarrow{BuLi} Ph_3\overset{\oplus}{P}—\overset{\ominus}{\ddot{C}}HCHO \xrightarrow[E\text{-selective}]{PhCHO} TM\ (6)$$

The synthesis of the *Z* unsaturated ester (7), for example, can be designed as follows:

Retrosynthetic analysis


MeO$_2$C
Wittig
MeO$_2$C
CHO
+ Ph$_3\overset{\oplus}{P}$–CH$_2$CH(CH$_3$)$_2$
P—C
Ph$_3$P + ClCH$_2$CH(CH$_3$)$_2$

TM (7)

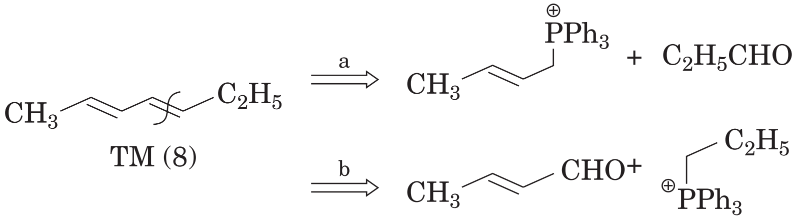
Synthesis

$$Ph_3P + ClCH_2CH(CH_3)_2 \xrightarrow{S_N2} Ph_3\overset{\oplus}{P}—CH_2CH(CH_3)_2\,Cl^{\ominus} \xrightarrow[2.\ MeO_2C(CH_2)_4CHO]{1.\ t\text{-}BuOK} TM\ (7)$$

2. Synthesis of conjugated dienes by the Wittig reaction

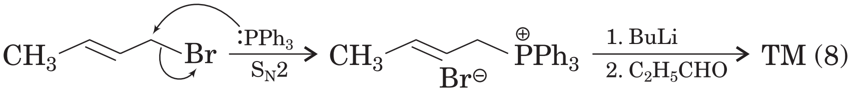
Conjugated dienes (8) can also be synthesized by the Wittig reaction. Both of the disconnections giving allylic phosphonium salts and simple aldehydes or unstabilized phosphonium salts and enals as starting materials are acceptable. If R^1 and R^2 are simple alkyl groups, the route (a) is likely to yield more *trans* double bond and the route (b) is likely to give more *cis* double bond. For example, the synthesis of (2*E*, 4*E*)-2,4-pentadiene (8) can be designed as follows:

Retrosynthetic analysis



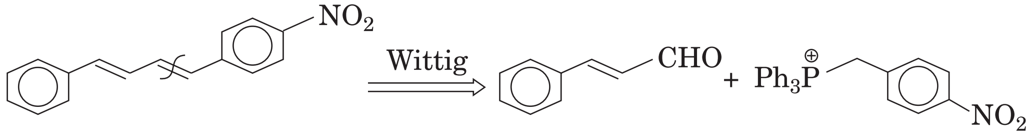
TM (8)

Synthesis



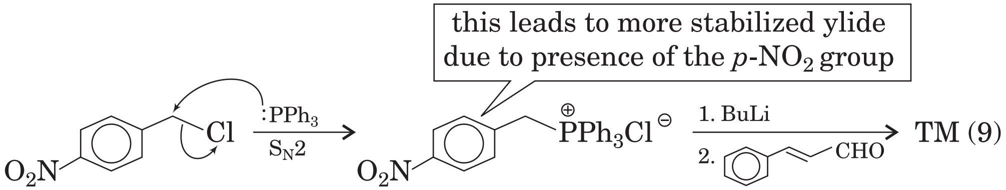
The alternative disconnection (b) is suitable for 1,4-diarylbutadiene (2) because it gives benzyl phosphonium salts (forming stabilized ylides) and easily prepared cinnamaldehydes. For example, the synthesis of the diene (9) can be designed as follows:

Retrosynthetic analysis



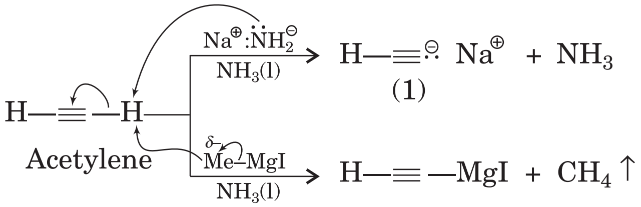
TM (9)

Synthesis

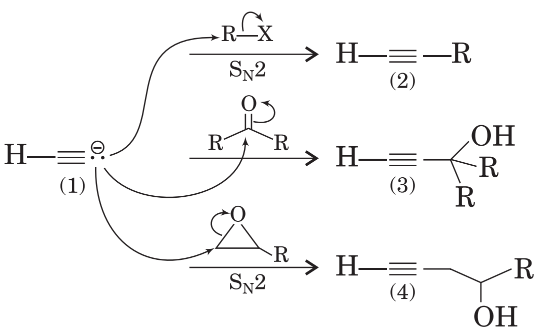

this leads to more stabilized ylide due to presence of the p-NO_2 group

3.1.9 Use of Acetylenes (Alkynes) in Organic Synthesis

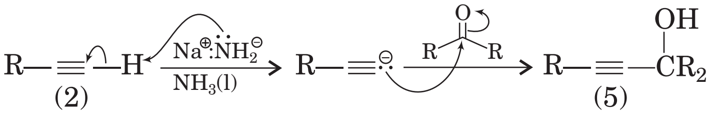
Acetylene itself is readily available and its most important property is its ability to form a carbanion usually with sodamide in liquid ammonia and with Grignard reagents. This is one of the few carbanions available as a genuine intermediate. The carbon in acetylene is *sp* hybridized. Due to more *s* character the carbon becomes more electronegative and causes weakening of the C—H bond. So, in the presence of a strong base, it acts as an acid.



The carbanion (1) reacts with alkyl halides, carbonyl compounds and epoxides to give the higher alkyne (2) and the unsaturated alcohols (3) and (4), respectively.

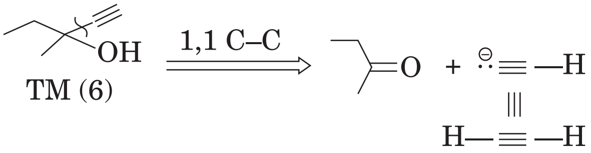


The resulting compounds with one more acetylenic proton react again with base and then with the electrophilic species to yield similar products. For example, (2) yields (5).

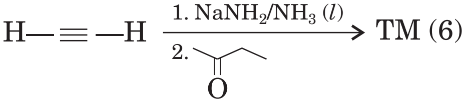


Therefore, disconnection of any bond next to a triple bond is reasonable. The synthesis of the tranquilliser oblivion (6) and the surfactant surfynol (7) can be designed as follows:

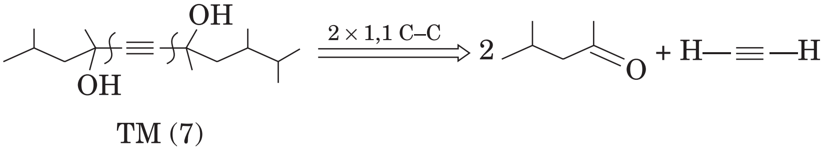
Retrosynthetic analysis



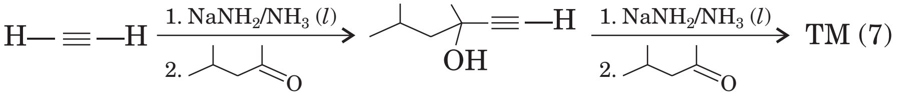
Synthesis



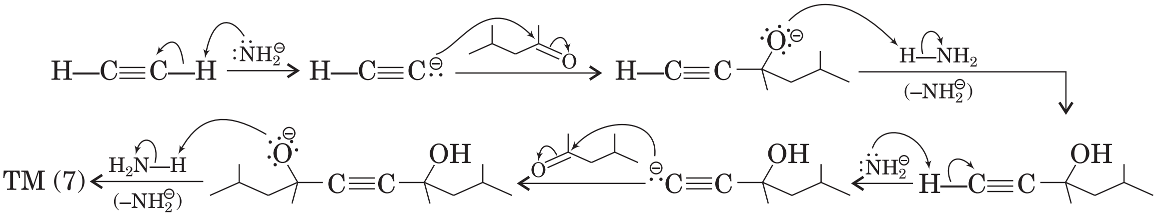
Retrosynthetic analysis



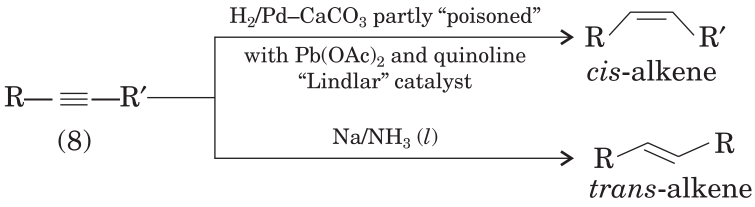
Synthesis

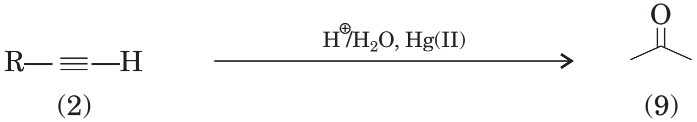


Mechanism:

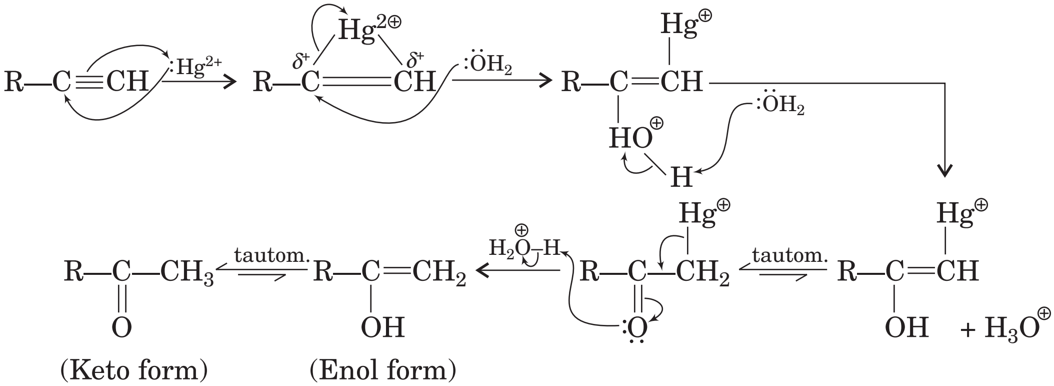


Some acetylene adducts are also valuable intermediates because disubstituted acetylenes (8) can be reduced to *cis* or *trans* alkenes as desired and because mono-substituted acetylenes (2) can be hydrated in the presence of dilute acid and Hg^{2+} to yield methyl ketones (9).



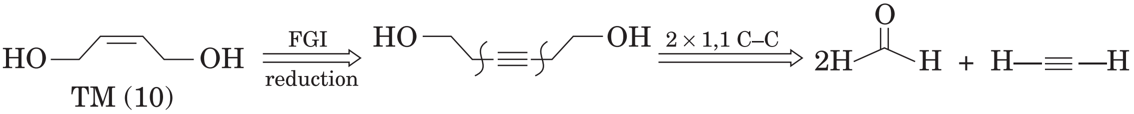


Mechanism:

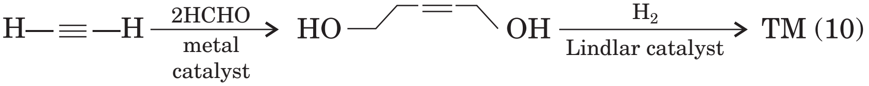


The synthesis of the important intermediate *cis*-butene diol (10) and the carnation perfume (11), for example, can be designed as follows:

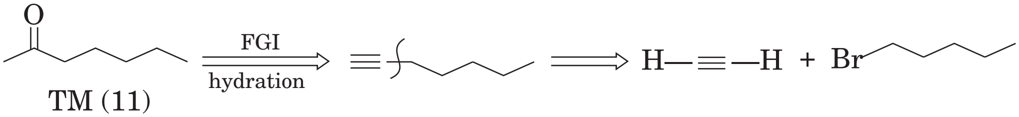
Retrosynthetic analysis



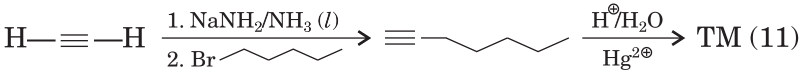
Synthesis



Retrosynthetic analysis

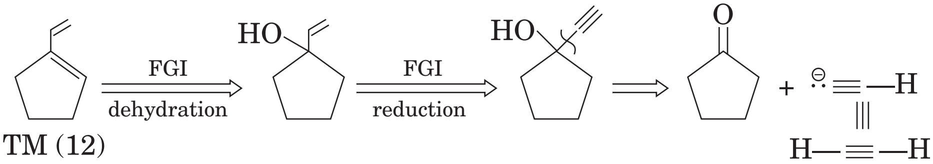


Synthesis

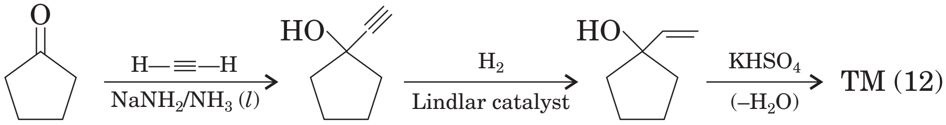


Acetylenes are particularly useful for synthesizing dienes of the type (12) and this is because the double bond outside the ring comes from acetylene and the double bond inside the ring is formed by dehydration of the corresponding alcohol. The synthesis of the diene (12), for example, can be designed as follows:

Retrosynthetic analysis



Synthesis

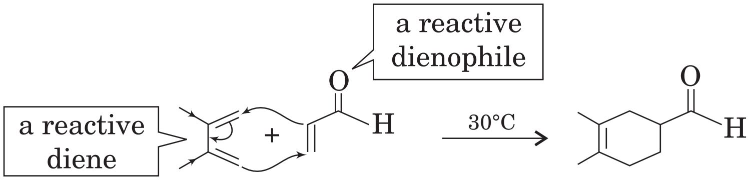


3.1.10 Two-Group C—C Disconnections

When two functional groups are used together to guide a disconnection, it is called a two-group C—C disconnection. These bifunctional disconnections are classified according to the relative distances between the two functional groups under consideration. For example, 1,2-, 1,3-, 1,4-, 1,5-, and 1,6-bifunctional disconnections. Since these are oxygen-containing functional groups, these are also abbreviated as 1,2-diO disconnection, 1,5-diO disconnection, and so on. However, 1,3-diO, 1,5-diO and 1,6-diO disconnections are quite convenient. The Diels-Alder reaction may also be considered as a two-group C—C disconnection.

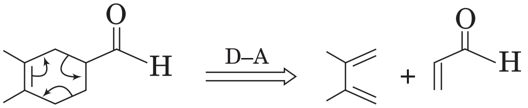
3.1.10.1 Diels-Alder Reaction

The Diels-Alder reaction (a pericyclic reaction) is one of the most important reactions used in organic synthesis and this is because it makes two C—C bonds concertedly, i.e., in one step and also because the reaction is regioselective as well as stereoselective. It is a (4 + 2)-cycloaddition reaction between a conjugated *diene* (a 4π-electron system) and a compound containing a double bond (a 2π-electron system) called a *dienophile* (diene + *philia*, Greek: to love) to form a six-membered ring (a cyclohexene) which is often called an *adduct*. In general, the most reactive dienophile is one in which the double bond is conjugated to some electron-attracting group while the more common reactive dienes are those which have electron-releasing groups bonded to the double bond. For example:



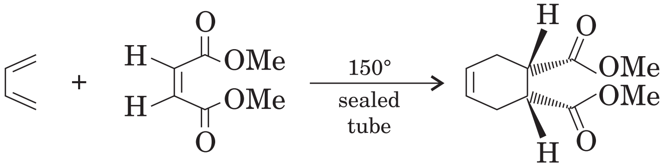
2,3-Dimethyl-1,3-butadiene Propenal (100%)

The disconnection corresponding to the above reaction (the Diels-Alder reaction) can be done by drawing the reverse reaction mechanism

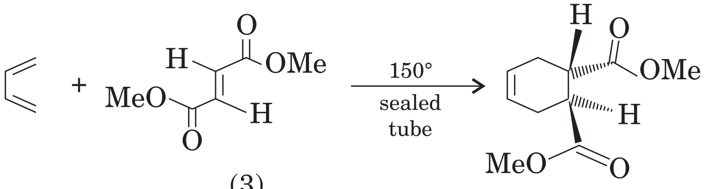


This is a two-group disconnection because it can be done only when both features—cyclohexene and the electron-withdrawing group—are present and the relationship between them is recognised. A Diels-Alder disconnection is, therefore, worth trying if a TM (simple or complicated) contains a cyclohexene and an electron-withdrawing group at the right relationship.

Stereospecificity The Diels-Alder reaction is a concerted reaction and so, neither the diene nor the dienophile has time to rotate. As a consequence, the stereochemistry of each reactants remains preserved in the adduct. Thus, with respect to the dienophile and the diene the addition is stereospecific and almost always *syn*, i.e., the Diels-Alder reaction is stereospecific. The *cis*-dienophile (1), for example, gives the *cis*-adduct (2) and the *trans*-dienophile (3), for example, gives the *trans*-adduct (4).

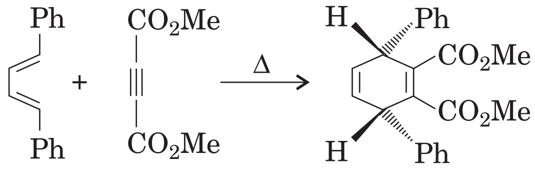


(1) (2)



(3) (4)

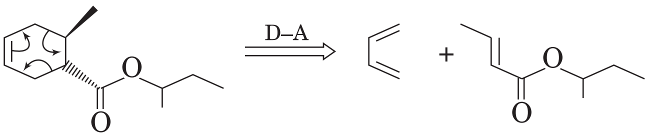
The stereochemistry of the diene is also transmitted to the product. This can be shown by the following reaction in which the diene (5) added to an acetylenic dienophile to give the *cis*-adduct (6).



(5) (6)

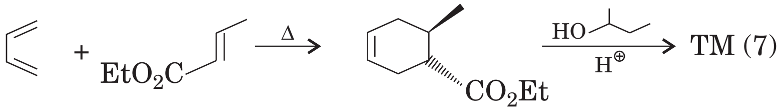
Since the synthetic attractant Siglure (7), used as bait for the Mediterranean fruit fly, has such a *trans* relationship between the substitutents at C-4 and C-5, the starting dienophile must be a *trans* one.

Retrosynthetic analysis

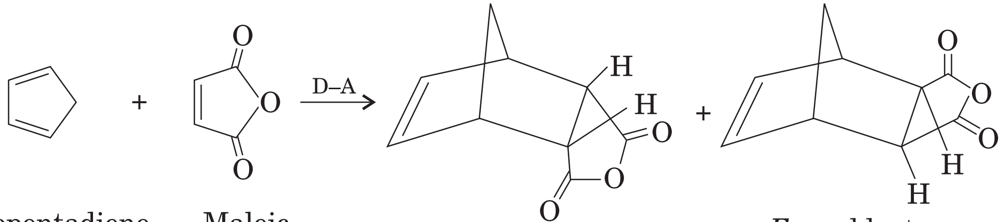


Siglure
TM (7)

Synthesis

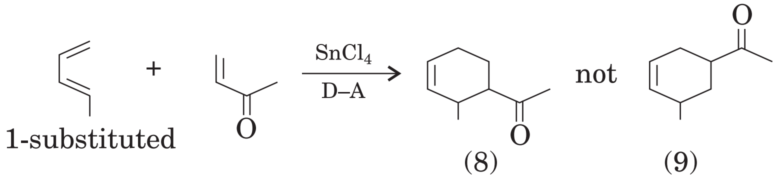


Stereoselectivity (*Endo*-selectivity) Though the stereochemistry of the diene and that of the dienophile is preserved in this reaction, in many cases two products can still be formed. This can be seen in cyclic systems. For example, when cyclopentadiene is allowed to react with maleic anhydride two diastereoisomeric products, called *exo* and *endo*, are obtained. However, the addiction gives the *endo*-adduct predominantly and this is because the *endo* transition state is stabilized by secondary orbital interactions (*see article no. 8.3.3.3*).

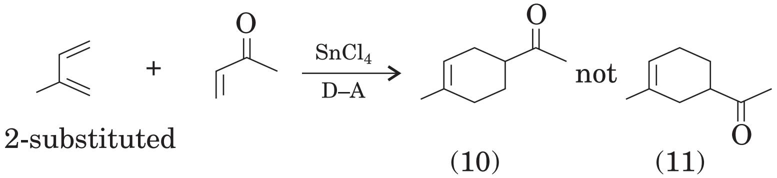


Cyclopentadiene Maleic anhydride *Endo*-adduct (major) *Exo*-adduct (minor)

Regioselectivity Diels-Alder reactions between unsymmetrical dienes and unsymmetrical dienophiles are regioselective. For example, 1-substituted butadienes give '*ortho*' products (8), whereas 2-substituted butadienes give '*para*' products (10), particularly in the presence of Lewis acid catalyst. The '*meta*' products (9, 11) cannot be prepared this way. For convenience, we may remember that the Diels-Alder reaction is '*ortho-para*' directing.



1-substituted (8) (9)

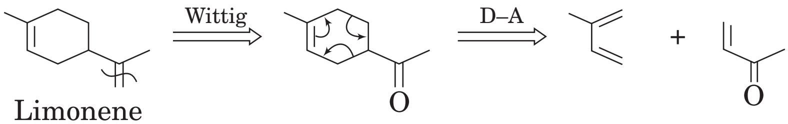


2-substituted (10) (11)

This can be explained in terms of charge distribution in each of the reactants.

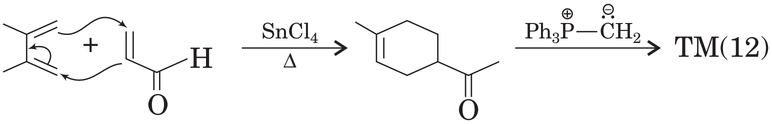
The synthesis of limonene (12), for example, can be designed as follows:

Retrosynthetic analysis



Limonene
(TM (12)

Synthesis

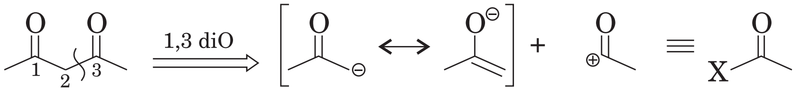


It is to be noted that stereospecificity, stereoselectivity, and regioselectivity combined give an unprecedented degree of control over the Diels-Alder reaction and that's why it is so much popular.

3.1.10.2 1,3-Difunctionlised Compounds and *α,β*-unsaturated Carbonyl Compounds

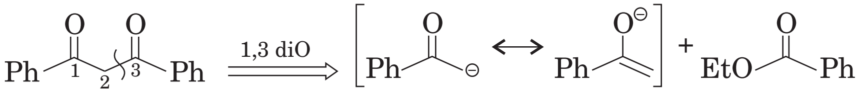
1,3-Difunctionalised compounds (compounds with two functional groups in a 1,3-relationship) can be disconnected easily as they give synthons with their natural polarity. The two important class of compounds having 1,3-relationship are dicarbonyl compounds and *β*-hydroxy carbonyl compounds (aldol systems). Since many aldol systems easily dehydrate to form *α*,*β*-unsaturated carbonyl systems, the 1,3-diO disconnection is also applicable to the *α*,*β*-unsaturated carbonyl systems.

1. 1,3-Dicarbonyl compounds These compounds have a wide range of applications. Disconnection of a 1,3-dicarbonyl compound gives an enolate anion and an acylium ion. Therefore, the corresponding forward reaction is the acylation of an enolate anion. This is possible with esters (X═OR) or acid chlorides (X═Cl).



The synthesis of dibenzoylmethane (13), for example, can be designed as follows:

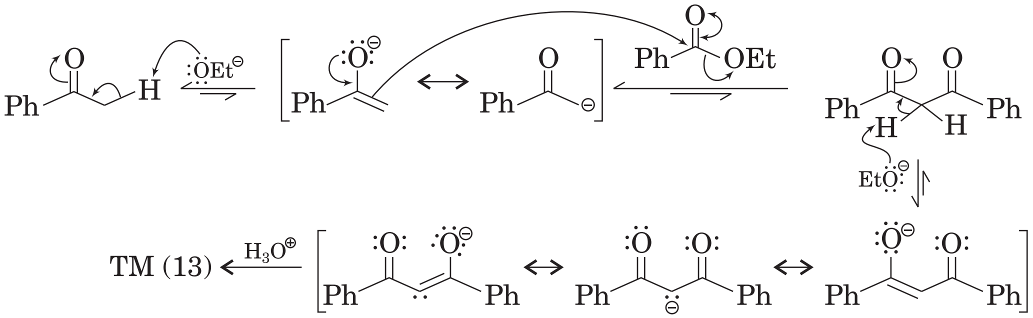
Retrosynthetic analysis



TM (13)

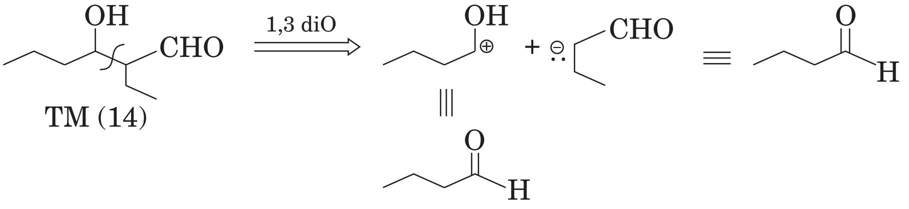
This disconnection which corresponds to a Claisen condensation gives simple starting materials.

Synthesis



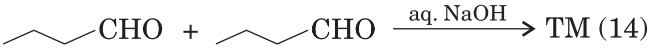
2. *β*-Hydroxy carbonyl compounds The same disconnection strategy is followed for *β*-hydroxy carbonyl compounds. In this disconnection at a lower oxidation level, the ester is replaced by an aldehyde or a ketone. Therefore, this disconnection actually corresponds to an *aldol reaction*. For example, the synthesis of the *β*-hydroxy aldehyde (14) can be designed as follows:

Retrosynthetic analysis

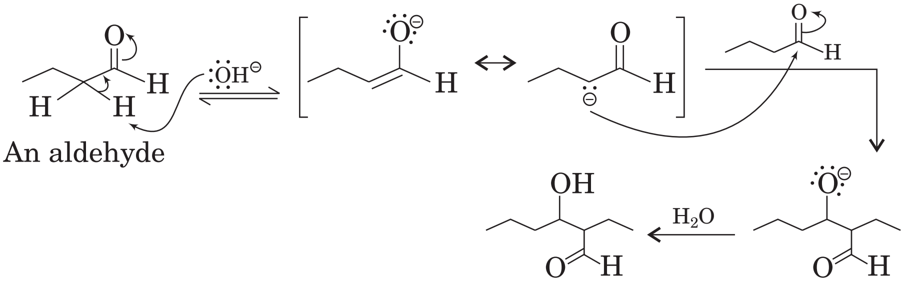


Therefore, this aldol (14) can be synthesized by aldolization of butanal .

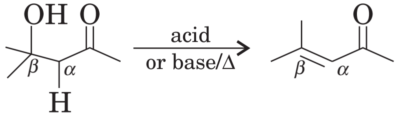
Synthesis



Mechanism:

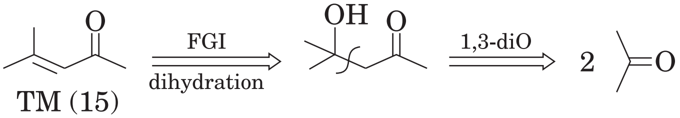


3. α,β-Unsaturated carbonyl compounds It is very easy to carry out dehydration of β-hydroxy carbonyl compounds and this is because the proton to be removed is enolic and the product formed is stabilized by conjugation.

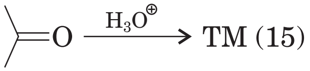


Therefore, the retrosynthetic analysis of an enone or other α,β-unsaturated carbonyl compounds must involve an FGI followed by a 1,3-diO disconnection. The dehydration takes place during the condensation so that the aldol need not be isolated. Under acidic conditions, dehydration occurs much rapidly. The synthesis of the enone (15), for example can be designed as follows:

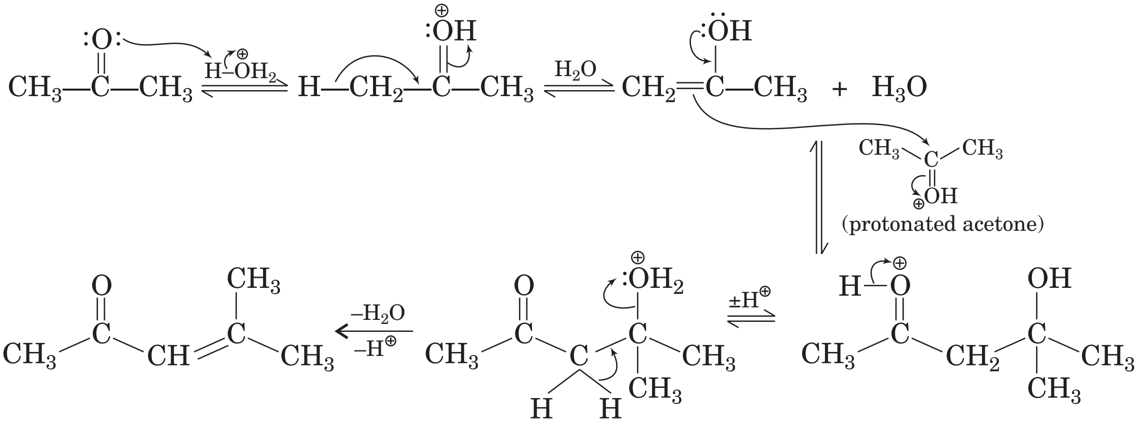
Retrosynthetic analysis


TM (15)

Synthesis

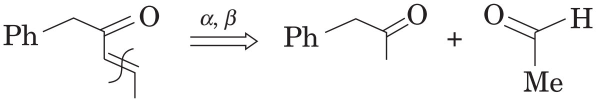


Mechanism:



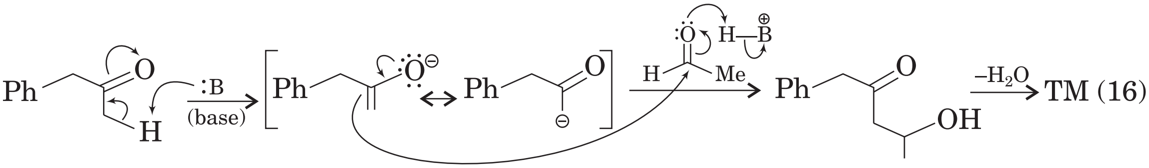
Problems related to chemoselectivity and regioselectivity in carbonyl condensations We have discussed some good disconnections based on carbonyl chemistry but avoided all questions of chemo- or regioselectivity. This becomes clear if we consider the synthesis of the enone (16).

Retrosynthetic analysis



TM (16)

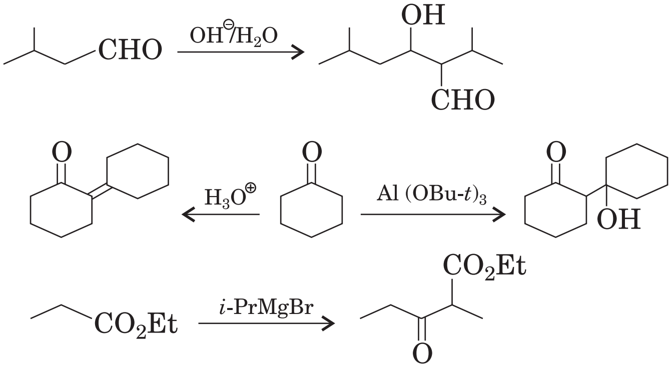
Synthesis



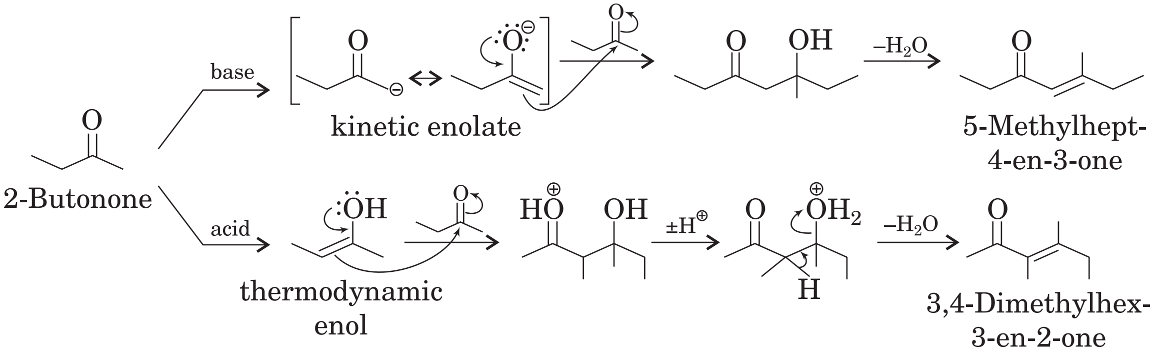
Although the retrosynthetic analysis of TM (16) is very simple, the corresponding synthesis is not very simple. In this synthesis, we want the ketone as the only carbonyl compound to enolise but the aldohyde can also enolise. We want to enolise on the methyl side of the ketone, but the benzyl side might be preferred because the corresponding enolate is more stabilized by resonance. We want the enolate to attack the aldehyde, but the enolate can also attack another molecule of ketone. Because of these ambiguity, carbonyl condensations give a mixture of products and become synthetically less useful. Hence, for a synthetically useful condensation there should be no ambiguity as to which compound enolises and which compound acts as the electrophile (chemoselectivity problem) nor any ambiguity on which side of the C═O group the enolization takes place (regioselectivity problem). Some methods to control both types of selectivity are discussed below.

Self-condensations We can solve the problem of chemoselectivity by using one type of carbonyl compound instead of two.

Aldehydes, symmetrical ketones and esters all give unambiguous reactions. For example

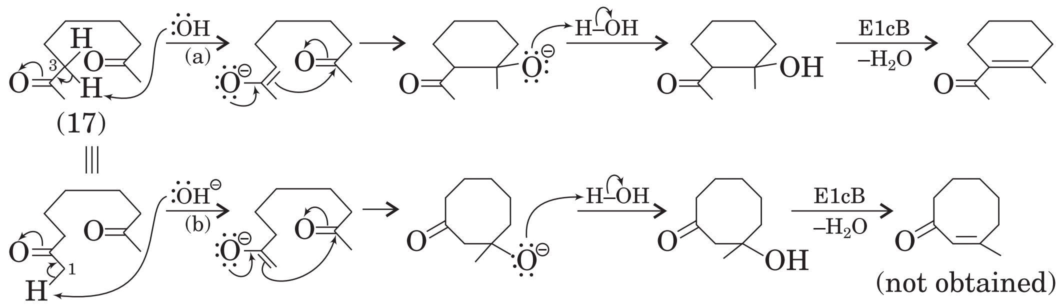


The problem of regioselectivity in enolisation of unsymmetrical ketones can be removed by changing the reaction conditions. Under basic conditions, there is a kinetic (or rate) control over the reaction; the more acidic proton, usually on the less substituted carbon, is removed to give the enolate. However, under acidic conditions, there is a thermodynamic control over the reaction; rapid equilibration between ketone and enol causes formation of highly substituted enol. Therefore, different products are formed in basic and acidic conditions from the unsymmetrical ketones. For example:



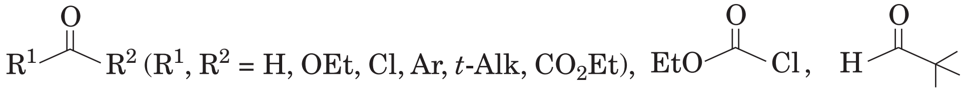
Therefore, if we want to get the 3-one, we have to carry out the reaction under basic conditions, and if we want to get the 2-one, the reaction should be carried out under acidic conditions.

Intramolecular reactions Although only one molecule is involved in intramolecular carbonyl condensations, the problem of chemoselectivity and regioselectivity may still arise. Since these carbonyl condensations are reversible, a thermodynamically preferred route is the one which leads to the formation of a five- or six-membered ring. Intramolecular reactions are, therefore, easier to control than the bimolecular equivalent. Cyclisation of the following symmetrical diketone (17) could take place in two ways [(a) and (b)] depending on which side of the ketone enolises. However, the reaction actually follows the route (a) only to yield a more stable six-membered ring rather than a less stable eight-membered ring. The same result in obtained in the presence of both acid and base.



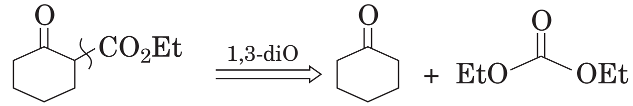
Cross-condensations

1. Use of compounds which cannot enolise Cross-condensation reactions are in general not synthetically useful when both the components contain enolisable H-atoms and this is because in that case a mixture of four products is obtained from which separation of the desired product becomes very difficult. Also, the yield of the desired product is not good. A compound, which cannot enolise, can react only as the electrophilic component in condensation reactions. A few examples are as follows:



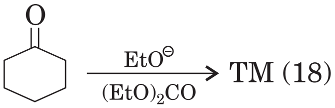
One synthetically useful case is the introduction of the activating group CO_2Et in compounds such as cyclohexanone. The synthesis of the ketoester (18), for example, can be designed as follows:

Retrosynthetic analysis

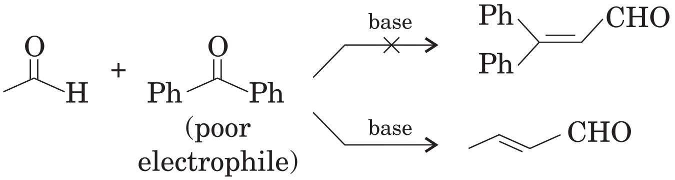


TM (18)

Synthesis

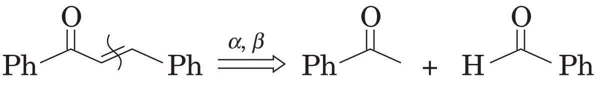


The carbonyl compound forming the enolate ion can also act as electrophile and self-condensation product will be formed. For example, when acetaldehyde is allowed to react with benzophenone in the presence of a base, no cross-condensation product is obtained.



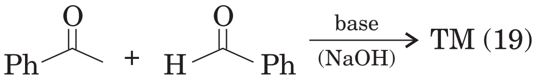
Therefore, to obtain the cross-condensation product exclusively, the electrophilic component must be more electrophilic than the enol component. Chalcone (19), for example, can be synthesised by considering these strategies of control. Only the ketone PhCOMe can enolise and the aldehyde PhCHO is more electrophilic among them.

Retrosynthetic analysis

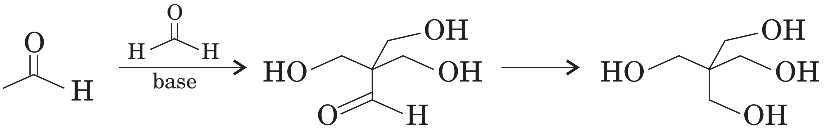


TM (19)

Synthesis

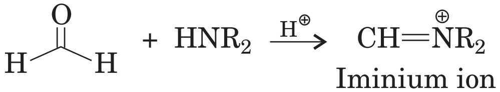


Formaldehyde, a non-enolisable carbonyl compound, is expected to be used as an electrophilic component in cross-condensations. However, the inconvenience with this compound is that it is too reactive and reacts repeatedly with the enol component to give a product (with no α-H) which then undergoes *Cannizzaro reaction*. For example

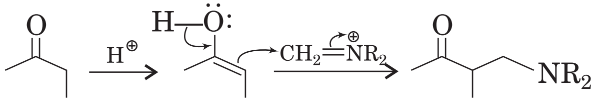


Pentaerythritol

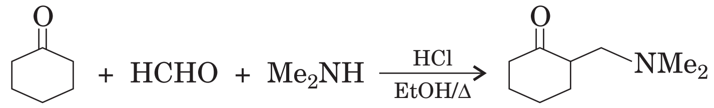
This problem can be avoided by using a formaldehyde equivalent which is less reactive than formaldehyde itself. A useful method is the *Mannich reaction* in which formaldehyde is allowed to react with the enolic component and a secondary amine. The initially formed iminium ion intermediate adds to the enol to form a Mannich base.



Iminium ion



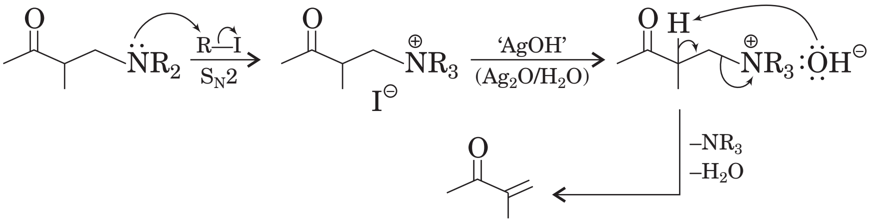
For example:



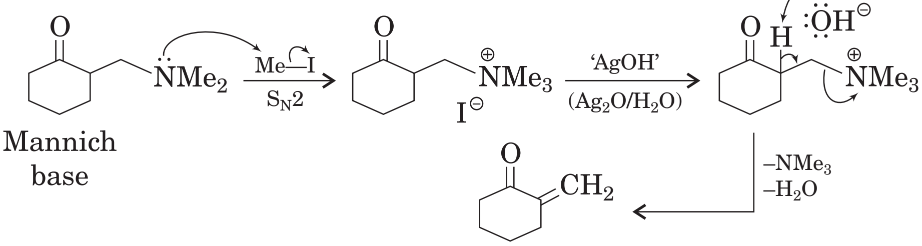
Cyclohexanone

Mannich base

Alkylation followed by elimination converts the Mannich base to the product of formaldehyde condensation.

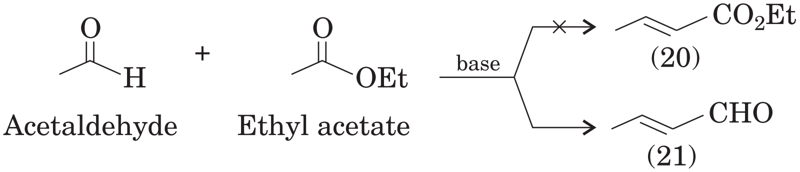


Example:



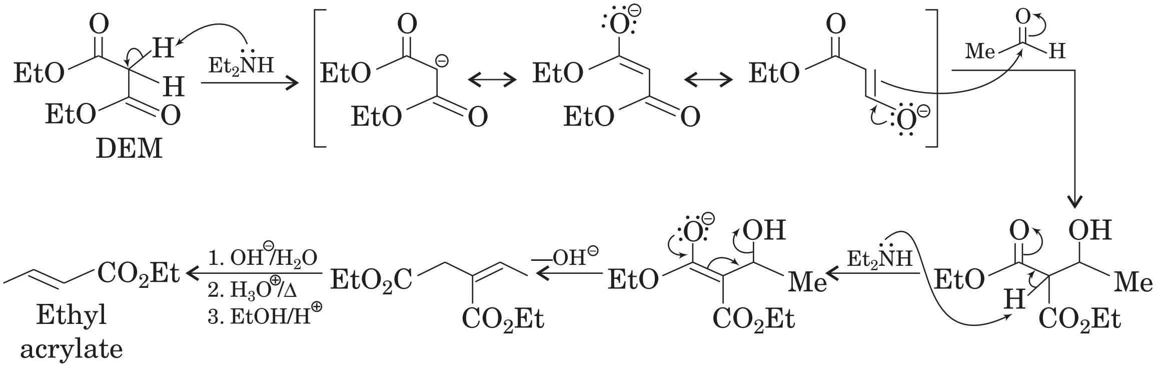
2. Use of specific enol equivalents Problems of regio- and chemoselectivity are all answered by the use of specific enol equivalents, i.e., reagents which behave as the regiospecific enol of one particular carbonyl compound. Condensation of the enol of an ester with an aldehyde as the electrophilic component is not at all effective as the aldehyde is more reactive in both senses and undergoes self-condensation to give the corresponding product (21).

Example:

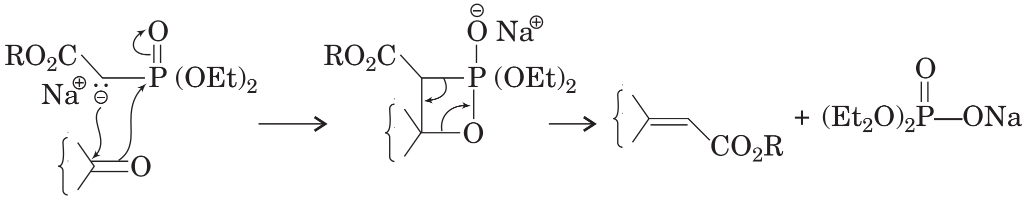


If malonate (DEM), the specific enol equivalent of the ester is used the condensation takes place smoothly.

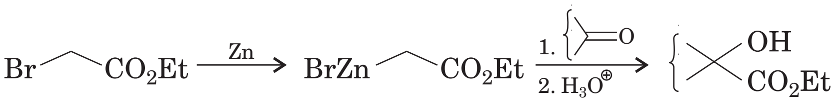
Under the reaction conditions malonate enolises completely while the aldehyde is only slightly enolised. The most electrophilic carbonyl group is still the aldehyde. A mixture of weak acid and weak base is often used as the conditions should be very mild to favour the kinetic control of product formation. This is what is called the *Knoevenagel condensation*. The product can be hydrolysed and decarboxylated in the usual way to yield the α,β-unsaturated ester.



Wittig reagents such as follows may be used as the specific enol equivalents.

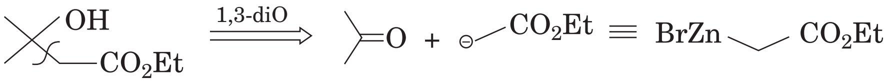


Organozinc reagents may also be used as specific enol equivalent. They react with aldehydes and ketones but not with esters, so they can be easily prepared from α-halo esters. Organozinc reagents obtained from α-halo esters react with aldehydes or ketones to form β-hydroxy esters. The reaction, known as the *Reformatsky reaction* may be outlined as follows:



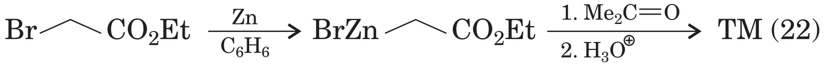
The synthesis of the β-hydroxy ester (22), for example, can be designed as follows:

Retrosynthetic analysis

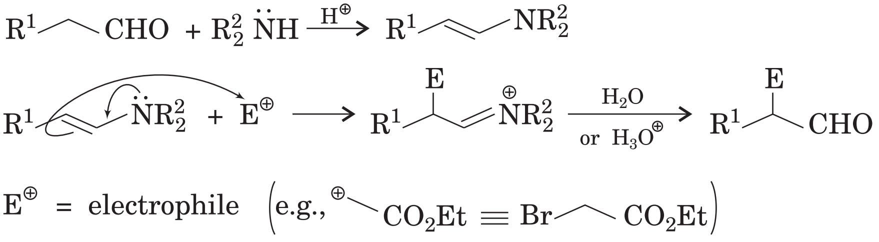


TM (22)

Synthesis

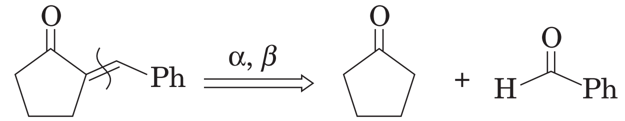


Enamines are the best specific enol equivalents for aldehydes. Also, these are useful for ketones. They can be easily prepared from carbonyl compound and secondary amine.



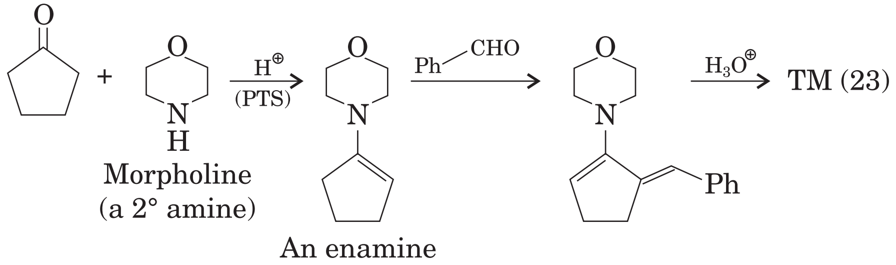
The retrosynthetic analysis of the enone (23) suggests that it is a condensation product of an aldehyde and the enol of a less reactive ketone. This condensation can easily be achieved by making the enamine of the ketone (the *Stork enamine reaction*).

Retrosynthetic analysis

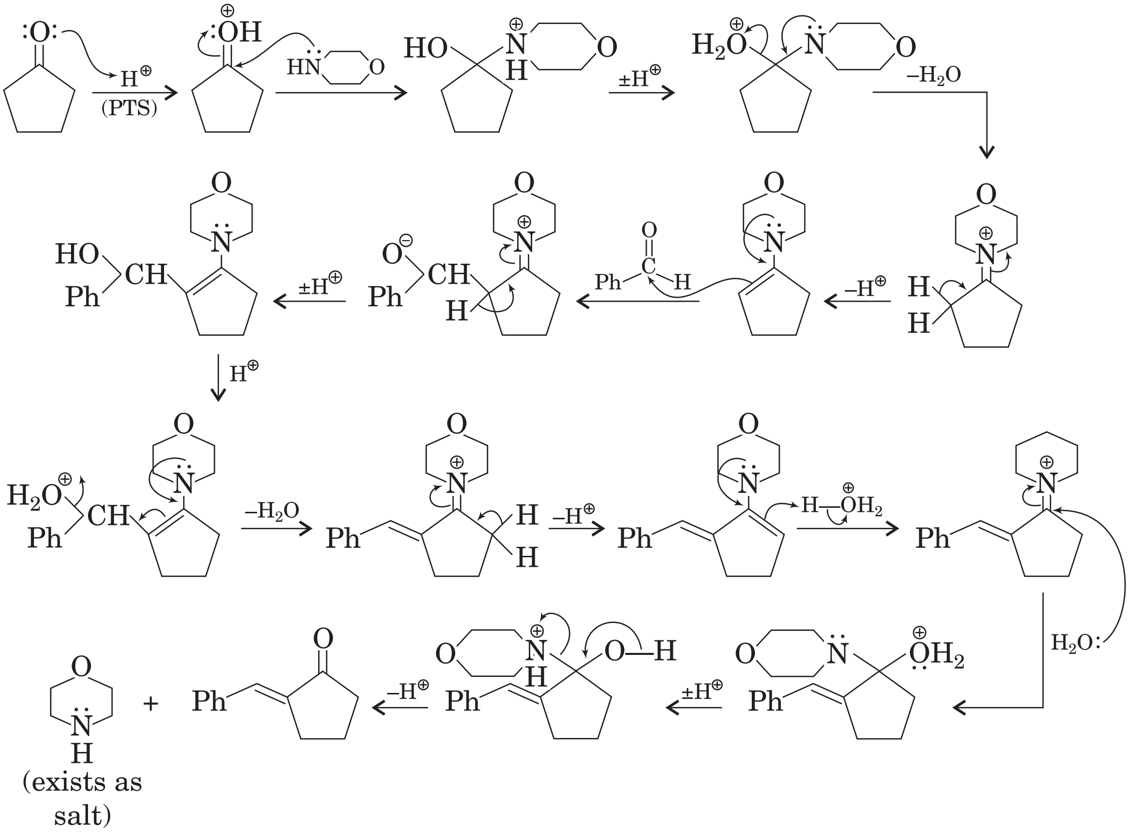


TM (23)

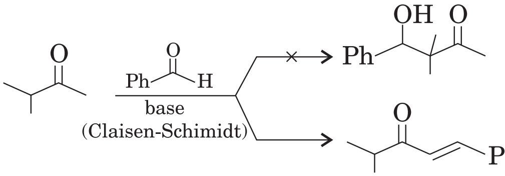
Synthesis



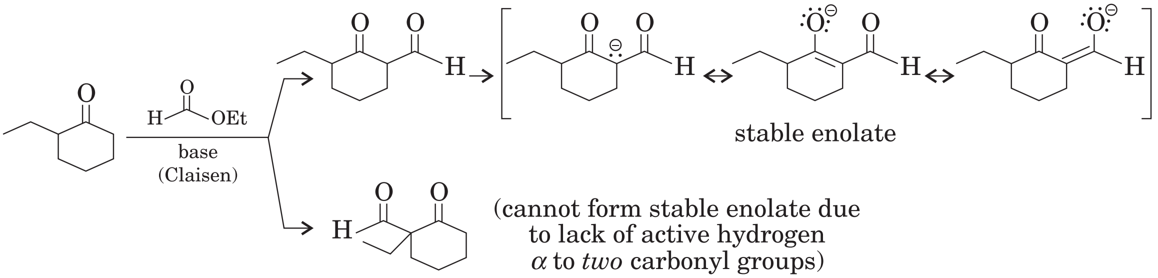
Mechanism:



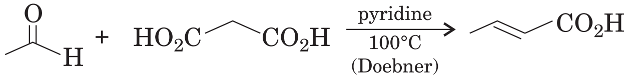
3. Removal of one product A very powerful method of thermodynamic control is the irreversible removal of one product when there established an equilibrium among the products. This type of control is commonly exercised through dehydration to thermodynamically more stable enones, product ionisation to give highly resonance-stabilized β-dicarbonyl anions or decarboxylative dehydration to give α,β-unsaturated carboxylic acids.



(cannot be dehydrated due to lack of α-H)



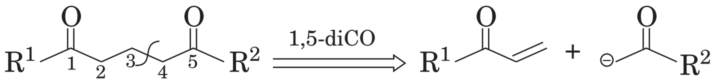
(cannot form stable enolate due to lack of active hydrogen α to *two* carbonyl groups)



3.1.10.3 1,5-Difunctionalised Compounds

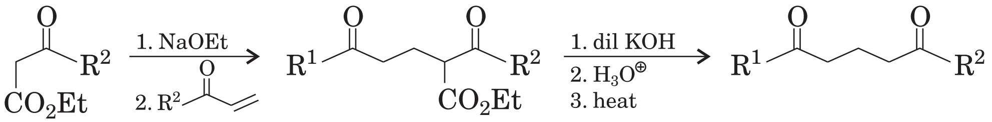
1,5-Dicarbonyl compounds can be disconnected at either α,β bond. The disconnection of this kind reveals that the target molecule can be synthesised by employing the well-known *Michael addition*.

Retrosynthesis analysis



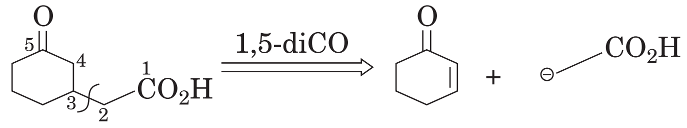
Since in this case all the questions of control remains, the enolate must have activating group like CO_2Et to ensure both enolisation at this site and Michael (i.e., 1,4) rather than direct (i.e., 1,2) addition to the α,β-unsaturated ketone.

Synthesis



Cyclic 1,5-difunctionised compounds are best disconnected where the chain meets the ring. For example, the synthesis of the keto acid (24) can be designed as follows:

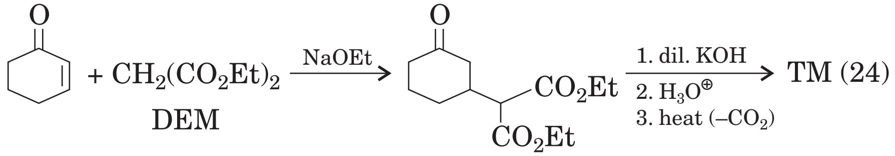
Retrosynthetic analysis



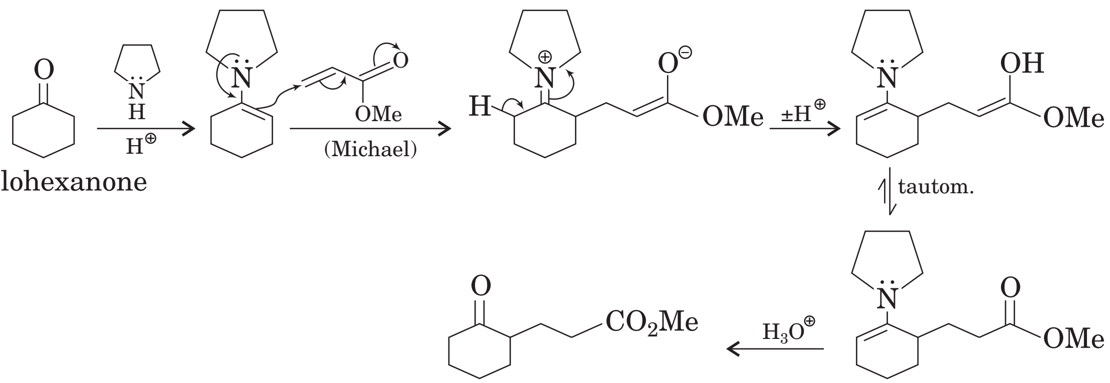
TM (24)

(activation required
and so DEM is used)

Synthesis

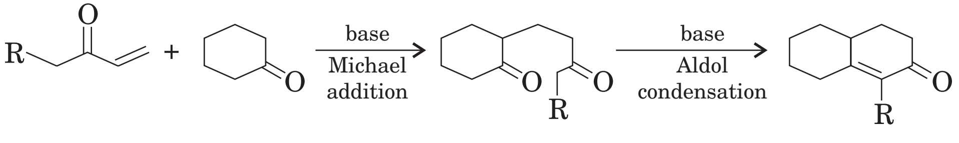


Activation by enamine formation We have already discussed the use of enamines as specific enol equivalents. They are found to be equally useful in Michael reactions. For example, the following keto ester (25) can be prepared from cyclohexanone through the formation of enanine.



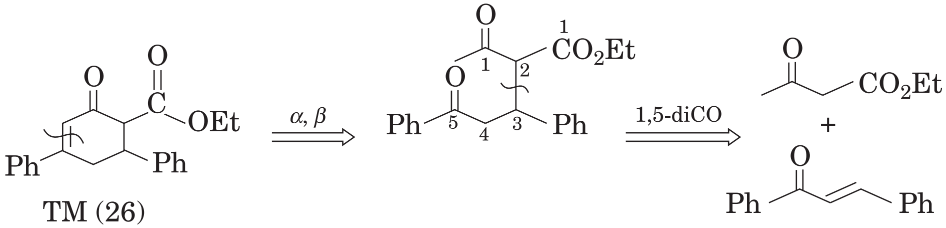
(25)

The Robinson annelation One extension of the Michael addition is an important way to make six-membered rings. The cyclisation in the second step of the synthesis often goes spontaneously and the whole process of addition and cyclisation, being a ring formation or annelation, is known as the *Robinson annelation*.



The compound (26) can be disconnected by following this strategy. Disconnection of the α,β-double bond reveals a simple 1,5-diCO disconnection.

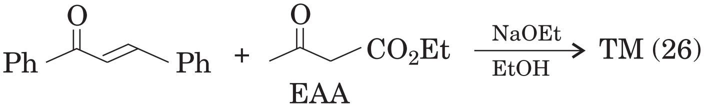
Retrosynthetic analysis



TM (26)

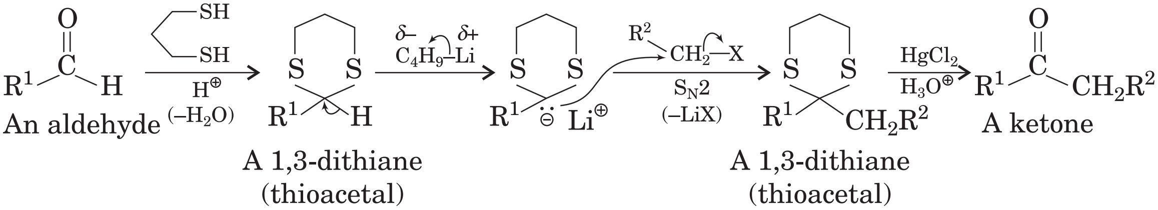
It is to be noted that if there is no CO_2Et group in the TM, its addition is necessary to control the Michael reaction.

Synthesis

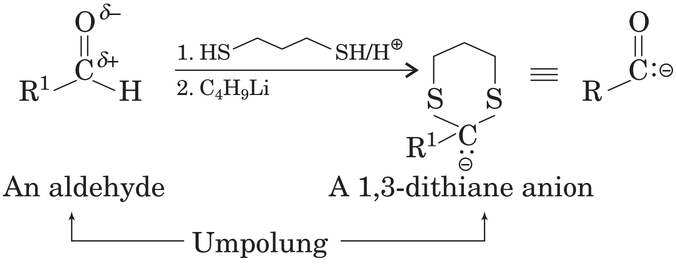


3.1.10.4 1,2- and 1,4-Difunctionalised Compounds: Concept of Umpolung and Latent Polarity

Concept of Umpolung (reversal of polarity) An aldehyde can be converted to a ketone through the formation of the corresponding 1,3-dithiane (a thioacetal) followed by alkylation of the dithiane and hydrolysis of the new thioacetal by dilute acid in the presence of Hg^{2+}.

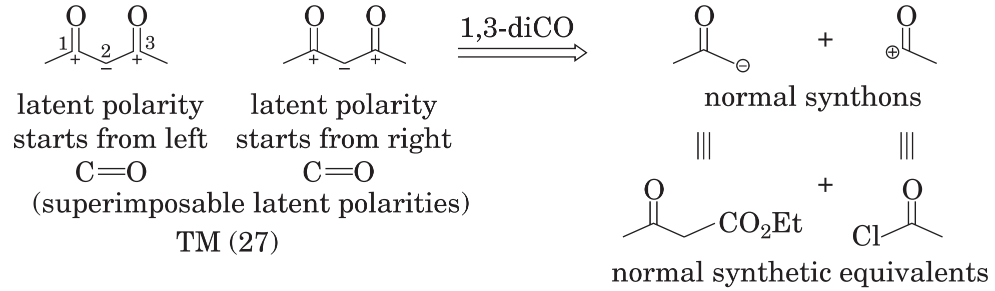


In these syntheses involving 1,3-dithiane, the usual mode of reaction of an aldehyde is reversed. The carbonyl carbon is positively polarized, i.e., normally it is electrophilic and so, it reacts with nucleophiles. When an aldehyde is converted to a 1,3-dithiane and then treated with butyllithium, the same carbonyl carbon becomes negatively charged and reacts with electrophiles. This reversal of polarity of the carbonyl carbon atom is called *umpolung* (German for 'polarity reversal'). The 1,3-dithiane anion is, therefore, a synthetic equivalent of an anionic carbonyl carbon atom (an aldehyde carbanion).

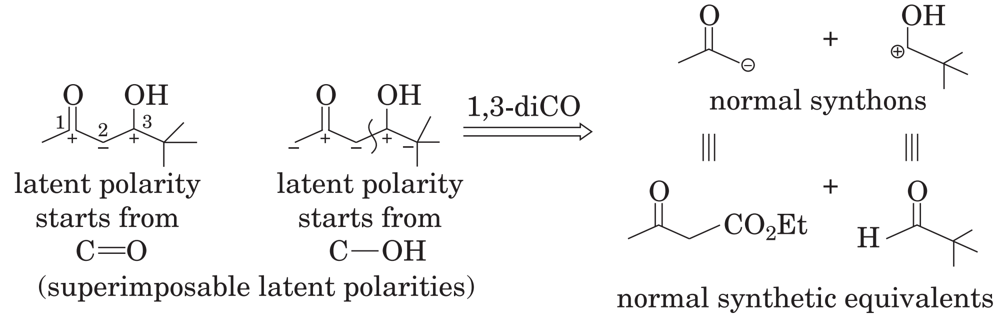


Concept of latent polarity The concept of latent polarity is actually an imaginary pattern of alternating (+) and (–) charges used to give an idea about the nature of synthons obtained as a result of disconnection of a target molecule. The polarities are arranged in such a way that the (+) charge is initially placed on the carbon adjacent to the more electronegative oxygen atom. There are two patterns of polarity in the molecules. These are discussed below:

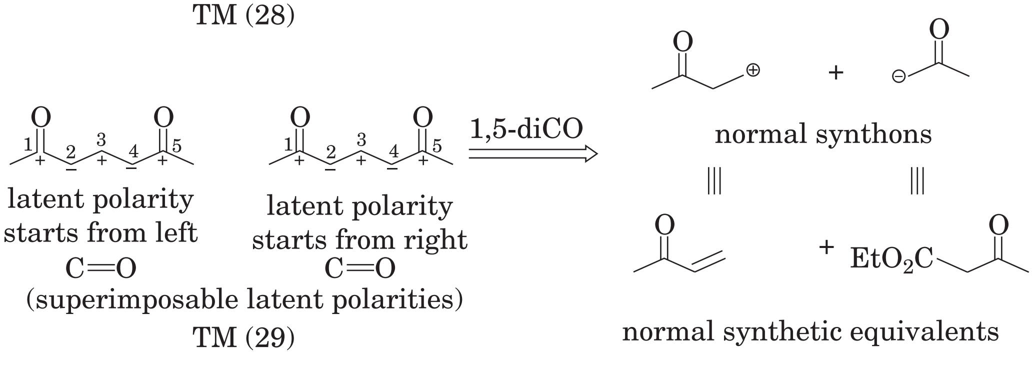
(a) Consonant pattern It is, in fact, a coincident relationship of latent polarities. If the latent polarities arising from each of the functional groups are added, they are found to be superimposable 1,3- and 1,5-DiO functional systems follow this charge pattern. In the following TM [TM(27) to TM (29)], for example, if we start either from left hand side C═O or from right hand side C═O/C—OH, we find that the relationship of latent polarities are overlapping, i.e., superimposable. When the target molecules of this type are disconnected, synthones of normal polarities are generated and as a consequence, the forward synthesis can be carried out smoothly with normal synthetic equivalents. This may be shown as follows:


O
O
1
2
3
+
–
+
O
O
+
–
+
1,3-diCO
O
⊖
+
O
⊕
latent polarity starts from left C═O
latent polarity starts from right C═O
(superimposable latent polarities)
normal synthons
|||
|||
O
CO₂Et
+
O
Cl
normal synthetic equivalents

TM (27)

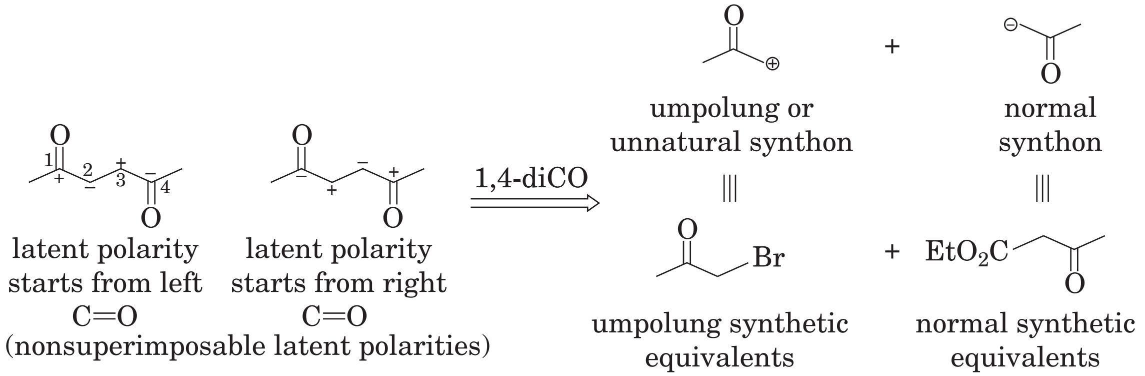

O
⊖
+
OH
⊕
normal synthons
O
OH
1
2
3
+
–
+
O
OH
–
+
–
+
–
1,3-diCO
latent polarity starts from C═O
latent polarity starts from C—OH
(superimposable latent polarities)
|||
|||
O
CO₂Et
+
O
H
normal synthetic equivalents

TM (28)

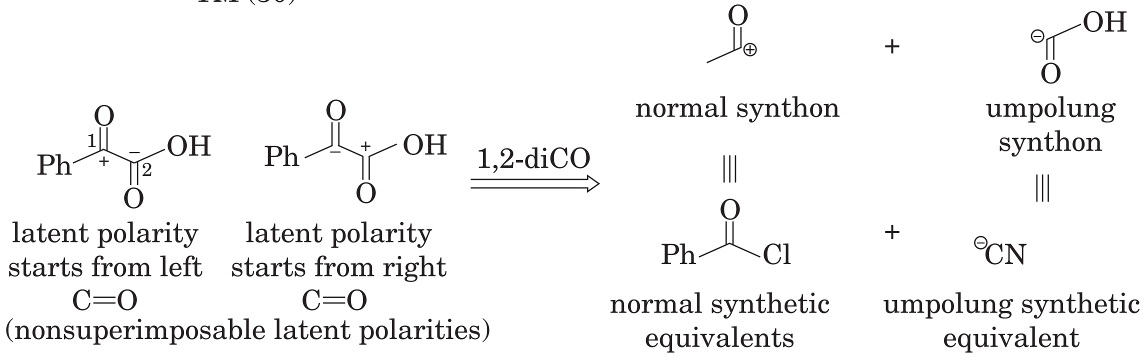

O
⊕
+
O
⊖
O
O
1
2
3
4
5
+
–
+
–
+
O
O
1
2
3
4
5
+
–
+
–
+
1,5-diCO
normal synthons
latent polarity starts from left C═O
latent polarity starts from right C═O
(superimposable latent polarities)
|||
|||
O
+
EtO₂C
O
normal synthetic equivalents

TM (29)

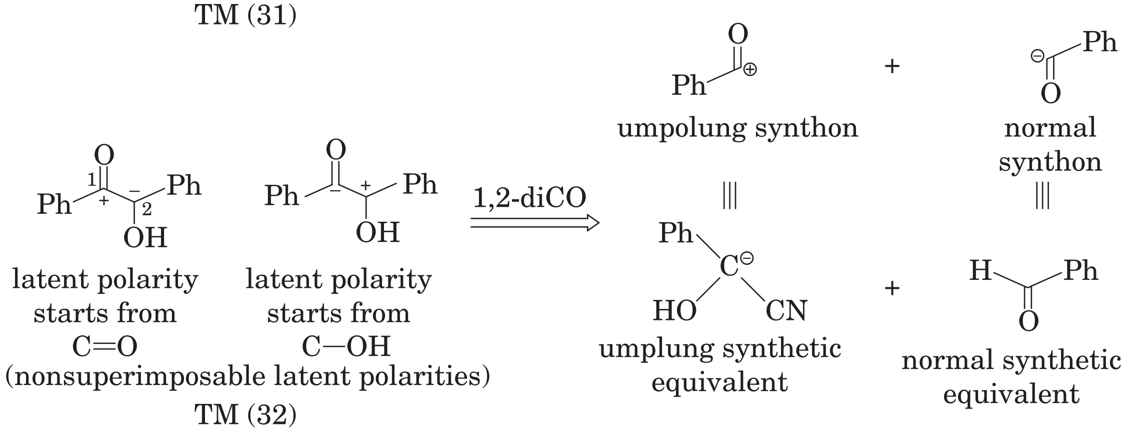
(b) Dissonant pattern It is a nonsuperimposable relationship of latent polarities. If the latent polarities arising from each of the functional groups are added, they are found to be nonsuperimposable. 1,2 and 1,4-DiO functional systems follow this charge pattern. For example, in the following TM [TM (30) to TM (32)], if we start either from the left hand side C=O or from the right hand side C=O/C—OH, we find that the latent polarities are not overlapping, i.e., not superimposable. On disconnection this type of TM must give synthons of unnatural polarity (umpolung synthones) and as a consequence, the forward synthesis requires umpolung synthetic equivalent or reagents. This may be shown as follows:


latent polarity starts from left C=O
latent polarity starts from right C=O
(nonsuperimposable latent polarities)
1,4-diCO
umpolung or unnatural synthon
normal synthon
Br
EtO_2C
umpolung synthetic equivalents
normal synthetic equivalents

TM (30)


Ph
OH
latent polarity starts from left C=O
latent polarity starts from right C=O
(nonsuperimposable latent polarities)
1,2-diCO
normal synthon
umpolung synthon
Cl
CN
normal synthetic equivalents
umpolung synthetic equivalent

TM (31)

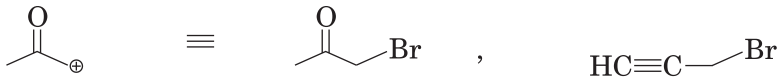

Ph
OH
latent polarity starts from C=O
latent polarity starts from C—OH
(nonsuperimposable latent polarities)
1,2-diCO
umpolung synthon
normal synthon
HO
CN
H
umplung synthetic equivalent
normal synthetic equivalent

TM (32)

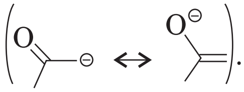
Illogical electrophiles and illogical nucleophiles When a bond of a TM is disconnected, two synthons are obtained which are ions either electrophilic or nucleophilic. If the normal polarity in a synthon is preserved, it is called a natural or normal synthon and the corresponding synthetic equivalent is called a natural or normal synthetic equivalent. On the other hand, if the normal polarity is reversed, the synthon is called an *unnatural* or *illogical synthon* and the corresponding synthetic equivalent is called *illogical synthetic equivalent*. The electrophilic illogical synthetic equivalents are generally designated as *illogical electrophiles* and the nucleophilic illogical synthetic equivalents are generally designated as *illogical nucleophiles*. All illogical synthons are also called *umpolung synthons* and all illogical synthetic equivalents are called *umpolung synthetic equivalents* or *reagents*.

Examples of illogical (unnatural) electrophiles:

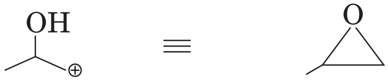
(i)



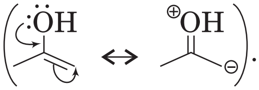
Illogical synthon (electrophilic) — Bromoacetone, Propargyl bromide: Illogical synthetic equivalents (electrophilic) or illogical electrophiles

The α-carbon atom of a carbonyl compound is normally nucleophilic . The α-carbon atom in bromoacetone is electrophilic in nature. The polarity is, therefore, reversed. So, bromoacetone is an illogical electrophile. Since the ethynyl group (HC≡C—) is the FGI of the acetyl group (CH_3CO—), propargyl bromide may also be considered as an illogical electrophile.

(ii)

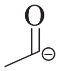


Illogical synthon (electrophilic) — Illogical synthetic equivalent (electrophilic) or illogical electrophile

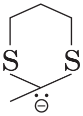
The α carbon atom of enol is normally nucleophilic . The epoxy carbon is highly electrophilic. The polarity, is, therefore, reversed in epoxide.

Examples of illogical (unnatural) nucleophiles:

(i)



≡

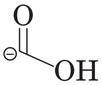


Illogical synthon (nucleophilic)

Illogical synthetic equivalent (nucleophilic) or illogical nucleophile

The synthon $CH_3\overset{\ominus}{C}O$ is illogical since the carbonyl carbon bears a negative charge in spite of being doubly-bonded to a more electronegative O atom $\left(\rangle C{=}O \leftrightarrow \rangle\overset{\oplus}{C}{-}\overset{\ominus}{O}\right)$. However, the same carbonyl carbon becomes nucleophilic, i.e., the polarity is reversed when an aldehyde is converted to a cyclic thioacetal (a dithiane derivative) and the thioacetal is treated with a base (which abstracts the hydrogen of the —CHO group).

(ii)



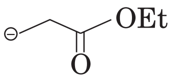
≡ $:\overset{\ominus}{C}\equiv N:$

Illogical synthon (nucleophilic)

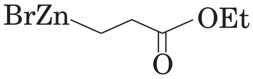
Illogical synthetic equivalent (nucleophilic) or illogical nucleophile

The synthon $\overset{\ominus}{C}OOH$ is illogical since the carbon bears a negative charge in spite of being bonded to two more electronegative oxygen atoms. However, it is nucleophilic in $:\overset{\ominus}{C}N$, i.e., the polarity is reversed.

(iii)

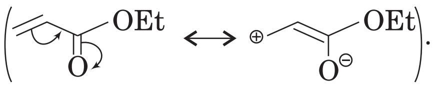


≡

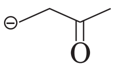


Illogical synthon (nucleophilic)

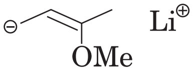
Illogical synthetic equivalent (nucleophilic) or illogical nucleophile

The β-carbon atom with respect to C=O is usually electrophilic . In the Reformatsky reagent, it is nucleophilic, i.e., the polarity is reversed.

(iv)

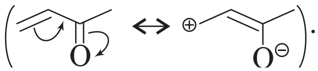


≡

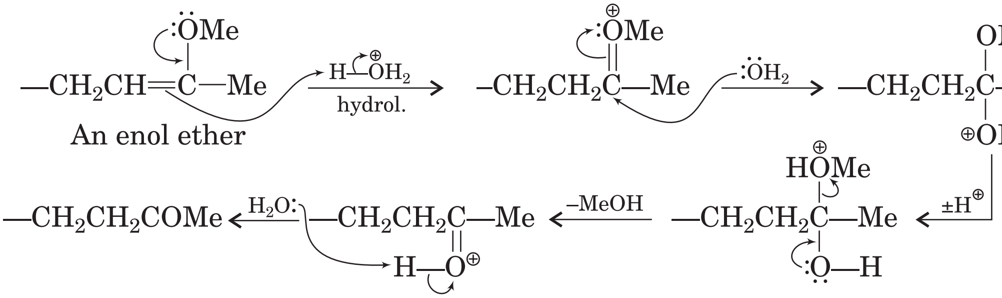


Illogical synthon (nucleophilic)

Illogical synthetic equivalent (nucleophilic) or illogical nucleophile

The carbon atom β to C=O is usually electrophilic .

The lithium salt is the corresponding illogical nucleophile because the —$CH_2CH{=}C(OMe)Me$ moiety is the FGI of the —$CH_2CH_2COCH_3$ group. This can be shown as follows:

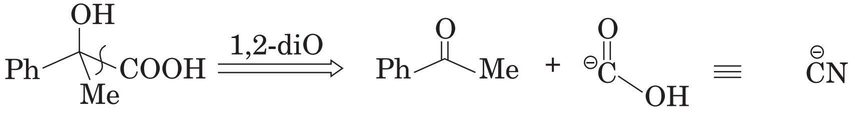


Syntheses involving umpolung synthetic equivalents or umpolung reagents are called *umpolung syntheses*.

Examples of illogical two-group disconnections

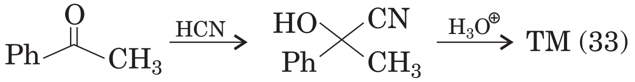
(a) 1,2-diO disconnection

1. *Retrosynthetic analysis*

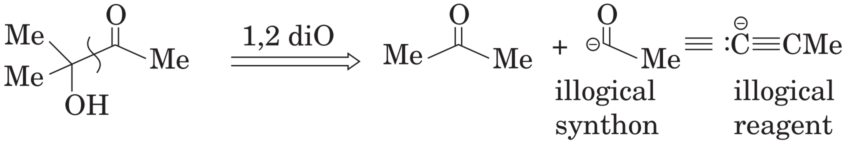


TM (33)

Synthesis

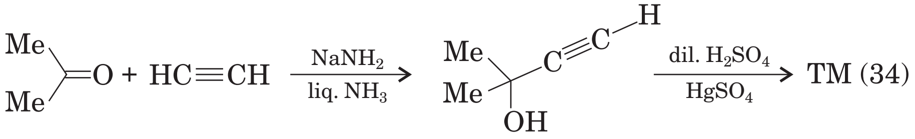


2. *Retrosynthetic analysis*

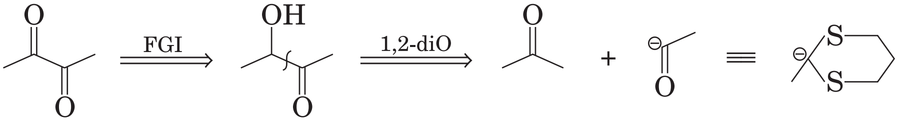


TM (34)

Synthesis

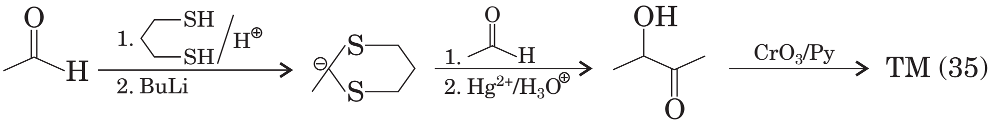


3. *Retrosynthetic analysis*



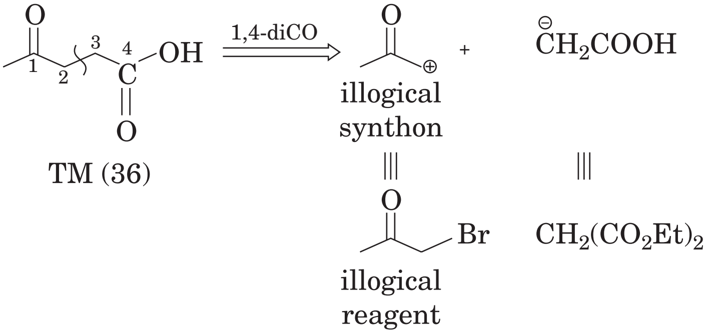
TM (35)

Synthesis

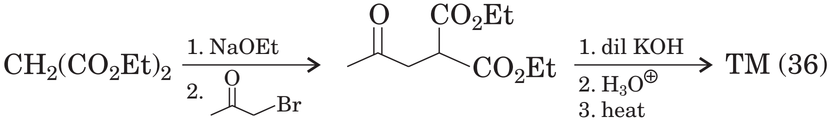


(b) 1,4-diO disconnection

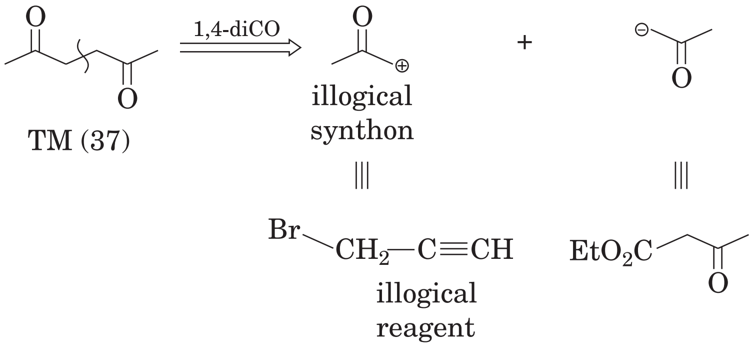
1. *Retrosynthetic analysis*



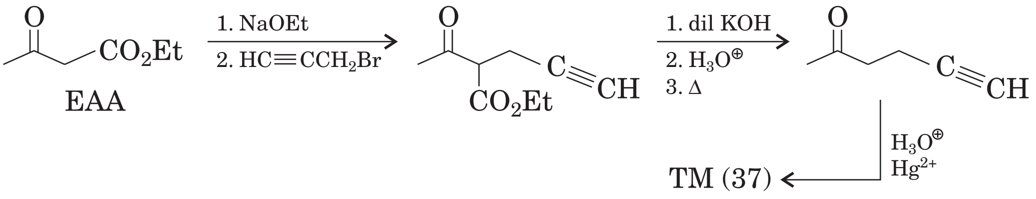
Synthesis



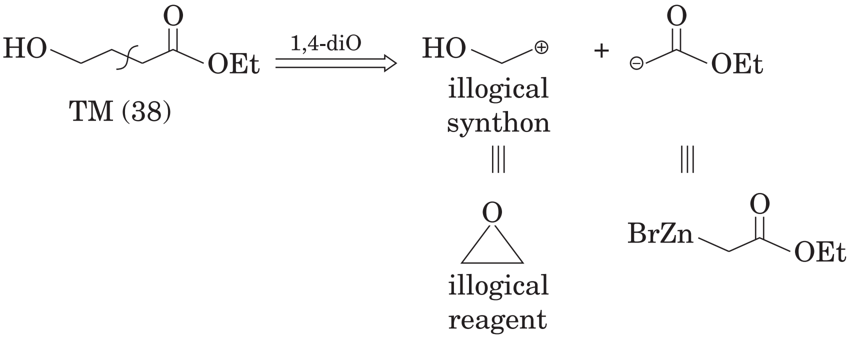
2. *Retrosynthetic analysis*



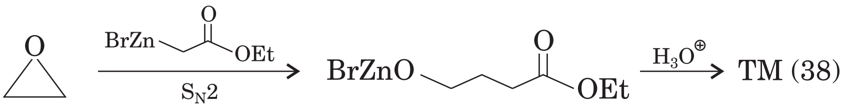
Synthesis



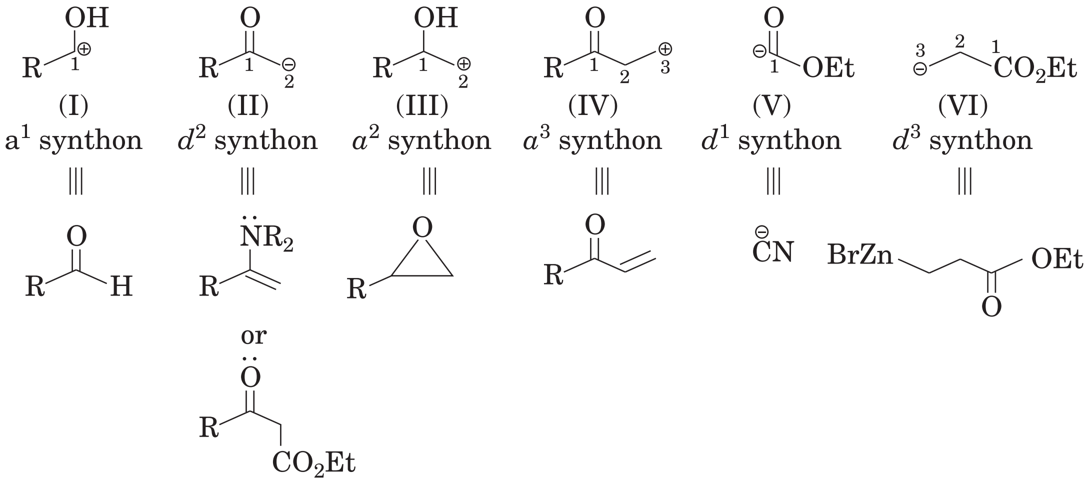
3. *Retrosynthetic analysis*



Synthesis



Donor and acceptor synthons A negatively polarized synthon in called a donor synthon (given the symbol '*d*') and a positively polarized synthon is called an acceptor synthon (given the symbol '*a*'). Classification of synthons can be made according to where the functional group is present in relation to the reactive site. For example, the synthon (I), which corresponds to an aldehyde, is called an a^1 synthon and this is because it is an acceptor that carries a functional group on the same carbon as its reactive centre. The synthon (II) is a d^2 synthon because it is a donor whose reacting site is at the 2-position relative to the C═O group. The synthons corresponding to an epoxide (III), a Michael acceptor (IV), cyanide ion (V) and the Reformatsky reagent (VI) can be classified as a^2, a^3, d^1, and d^3 synthones, respectively.



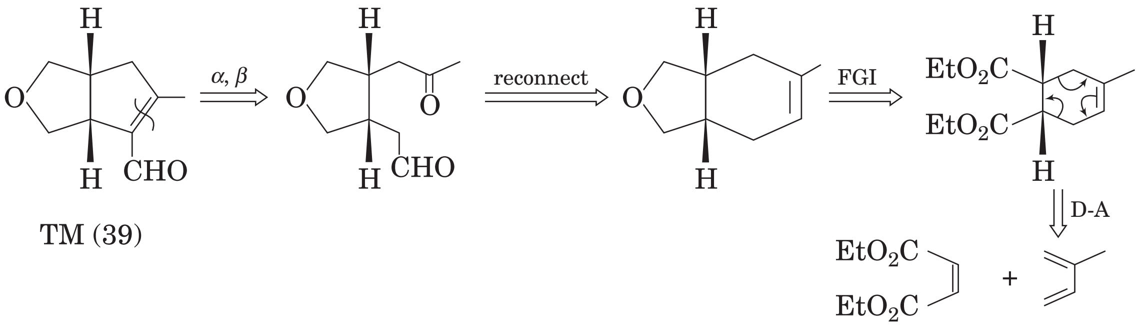
It is easy to design the synthesis of 1,3 and 1,5-difunctionalised compounds compared to 1,2- and 1,4-difunctionalised compounds. This can be explained on the basis of the type of synthon obtained on disconnection of such compounds. 1,3- and 1,5-difunctionalized compounds arise from $a^1 + d^2$ or from $a^3 + d^2$ combinations. These strategies correspond to the 'natural reactivity' of carbonyl compounds [alternating donor and acceptor properties along the chain) and therefore, require natural synthons. On the other hand, 1,2- and 1,4-difunctionalized compounds arise from $d^1 + a^3$, $a^1 + d^3$, $d^2 + a^2$ and $a^3 + d^1$ combinations. Therefore, these strategies required one natural synthon and one with umpolung (illogical) and these strategies are actually more difficult to realise with the common reagents. For this reason, it is easier to design the synthesis of 1,3- and 1,5-difunctionalized compounds compared to 1,2- and 1,3-difunctionalized compounds.

3.1.10.5 Reconnection: Synthesis of 1,6-difunctionalised Compounds

Reconnection is the usual strategy for synthesizing 1,6-difunctionalised compounds since the cyclohexenes required for the oxidative cleavage can easily be prepared. The most important way to make cyclohexenes is by the Diels-Alder reaction and this opens up a wide field of 1,6-dicarbonyl products. Reconnection strategy is also applicable in the synthesis of hydroxy esters.

Some examples of synthesising 1,6-difunctionalised compounds following reconnection strategy are given below:

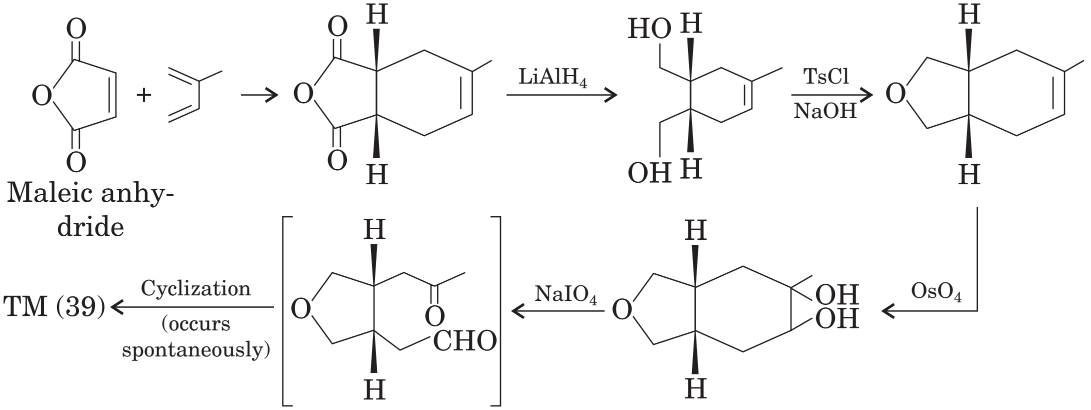
1. *Retrosynthetic analysis*



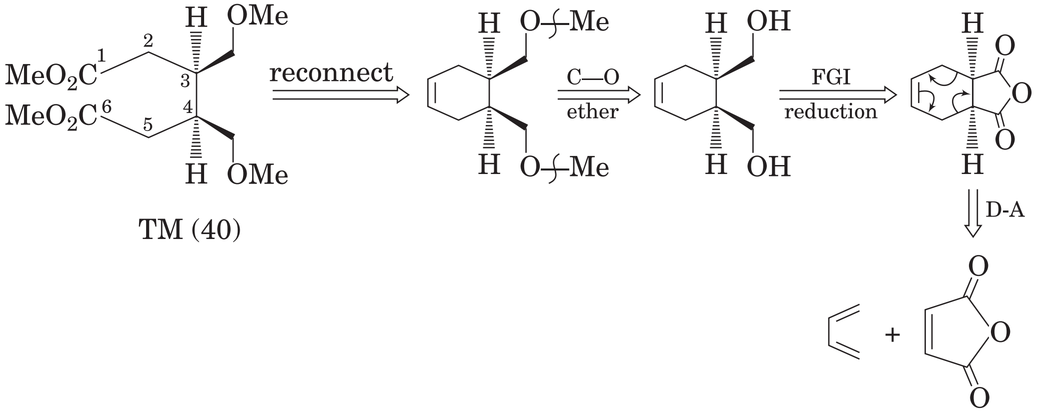
TM (39)

Synthesis

A successful synthesis by this route actually uses maleic anhydride as the dienophile.

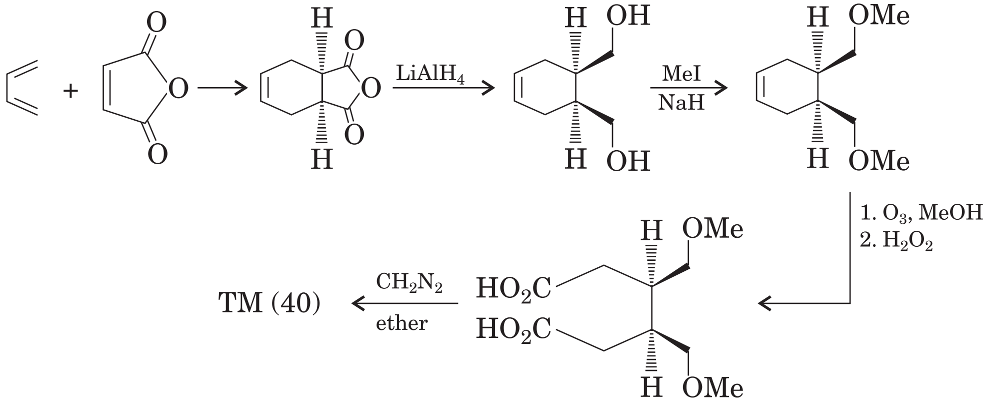


2. *Retrosynthetic analysis*

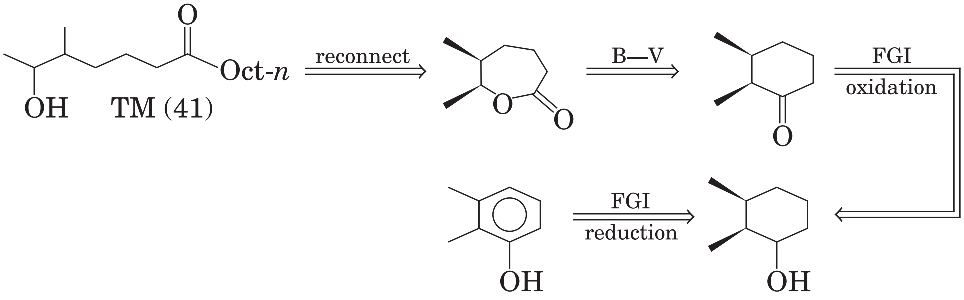


TM (40)

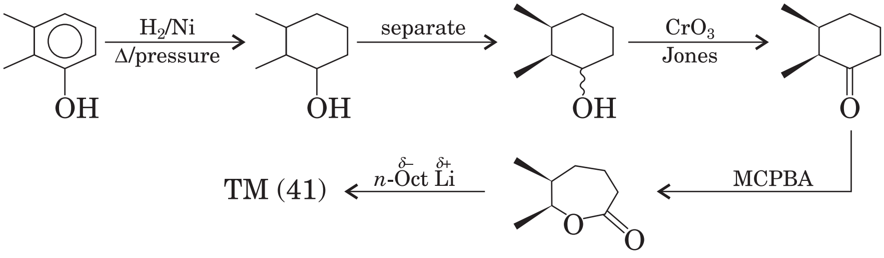
Synthesis



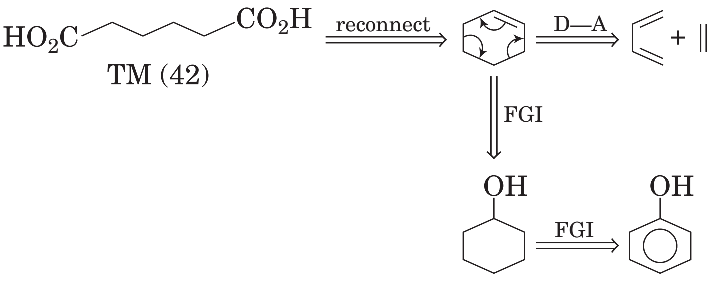
3. *Retrosynthetic analysis*



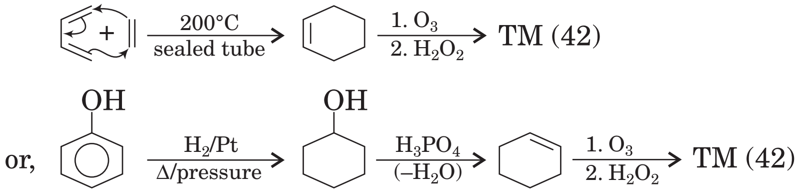
Synthesis



4. *Retrosynthetic analysis*



Synthesis



3.1.11 Amine Synthesis

A problem which is to be faced during the synthesis of amines is that the product of the reaction is usually more reactive than the starting material and so, it reacts further with the alkyl halide, i.e., there is a possibility of polyalkylation. Therefore, the C—X disconnection used for ethers, sulphides, etc. is not satisfactory.

Retrosynthetic analysis

$$R{-}NH{-}Me \xRightarrow{C-N} RNH_2 + MeI \quad \text{(not useful)}$$

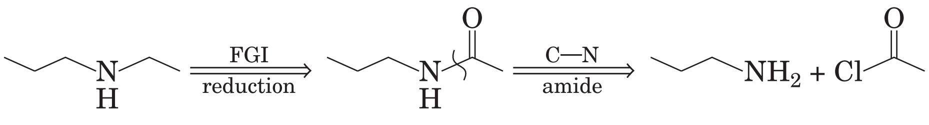
Synthesis

$$\underset{1^\circ\text{ amine}}{RNH_2} \xrightarrow[\substack{S_N2\\(-HI)}]{MeI} \underset{2^\circ\text{ amine}}{R\,NHMe} \xrightarrow[(-HI)]{MeI} \underset{3^\circ\text{ amine}}{R\,NMe_2} \xrightarrow{MeI} R\,\overset{\oplus}{N}Me_3\overset{\ominus}{I}$$

It is no use adding only one equivalent of MeI since the initially formed 2° amine completes with the 1° amine for MeI (because of electron-releasing +I effect, the N atom in 2° amine is more electron rich and hence, nucleophilic).

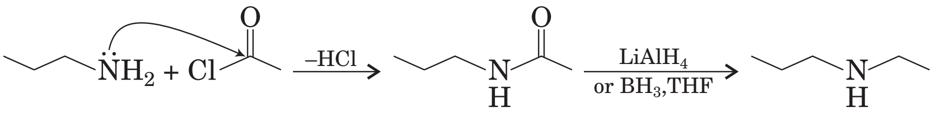
When electrophiles are used, they, unlike alkyl halides, give relatively unreactive products with amines. Acyl halides, aldehydes and ketones are the best examples. The products, amides and imines, can easily be reduced to amines. The imine route involving ketones is suitable for branched chain amines. An initial FGI, is, therefore, required before the C—N disconnection. For example:

(i) *Retrosynthetic analysis*

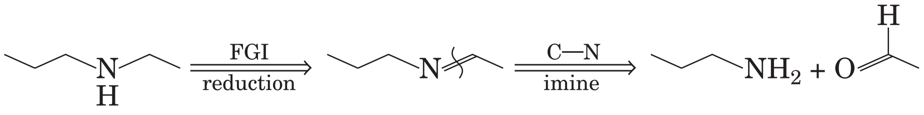


TM (1)
A 2° amine

Synthesis



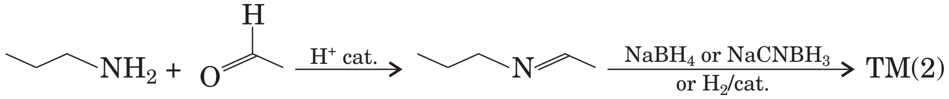
(ii) *Retrosynthetic analysis*



TM (2)

This approach is known as *reductive amination.*

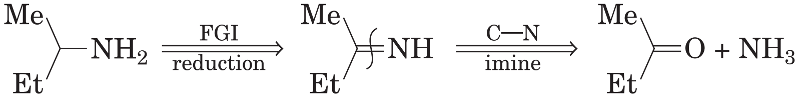
Synthesis



Synthesis of primary amines

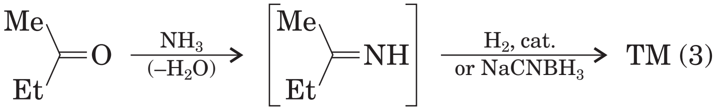
1. Primary amines can be prepared in a one-step reductive amination in which the unstable imine is not isolated. For example

   Retrosynthetic analysis



TM (3)

Synthesis



2. Unbranched primary amines are usually made by reduction of cyanides. This procedure is very suitable for benzylic amines since aryl cyanides can be prepared easily from diazonium salts and for homologous amines since $CN^{\ominus}$ ion (a good nucleophile) reacts easily with benzyl halides. In this case, the disconnection requires a preliminary FGI which is reasonable one because the reduction of —CN ⟶ $—CH_2NH_2$ is quite reliable. For example

   Retrosynthetic analysis

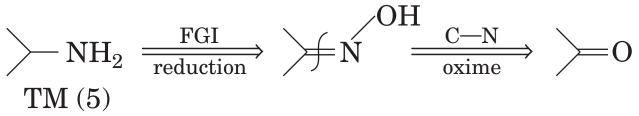
$$\underset{\text{TM (4)}}{\text{Ph }CH_2NH_2} \xRightarrow[\text{reduction}]{\text{FGI}} \text{Ph}\nmid\text{CN} \xRightarrow{\text{1,1 C—C}} \text{Ph—}\overset{\oplus}{N}_2 + CN^{\ominus}$$

Synthesis

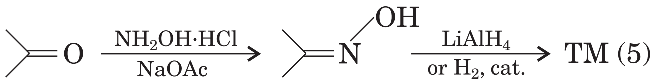
$$\text{Ph—}NH_2 \xrightarrow[\text{0–5°C}]{NaNO_2/HCl} \text{Ph—}\overset{\oplus}{N}_2 \xrightarrow{CuCN} \text{Ph—CN} \xrightarrow[H^{\oplus}]{H_2/Pd\text{—}C} \text{TM (4)}$$

3. Branched chain primary amines can be prepared through the formation of ketooximes followed by their reduction. For example:

Retrosynthetic analysis

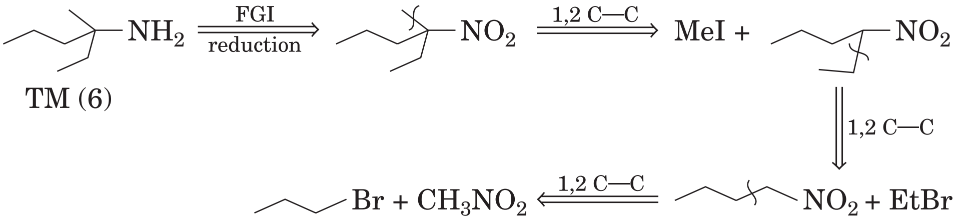


Synthesis

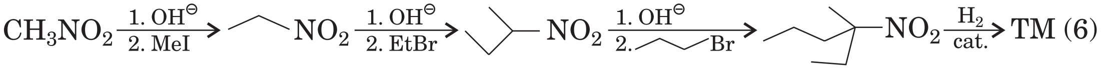


4. A 3° alkyl group containing primary amine can be prepared by alkylation followed by reduction of the aliphatic nitro compound. Another method involves the *Ritter reaction* followed by hydrolysis of the resulting amide. For example:

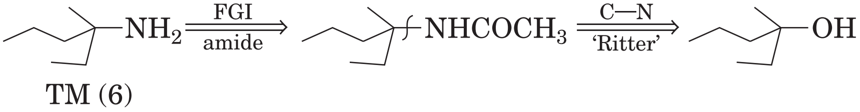
Retrosynthetic analysis (I)



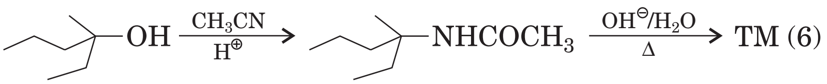
Synthesis



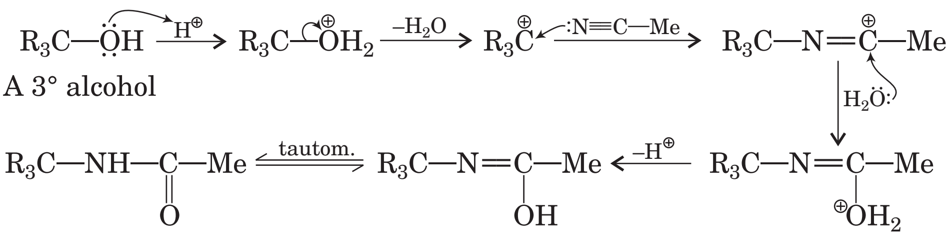
Retrosynthetic analysis (II)



Synthesis



Mechanism of 'Ritter reaction':



5. Primary amines may also be prepared by the reduction of azide. the azide ion, $N_3^{\ominus}$, acts as a reagent for $NH_2^{\ominus}$, so that the disconnection is the normal one for C—X bond.

   For example:

   Retrosynthetic analysis

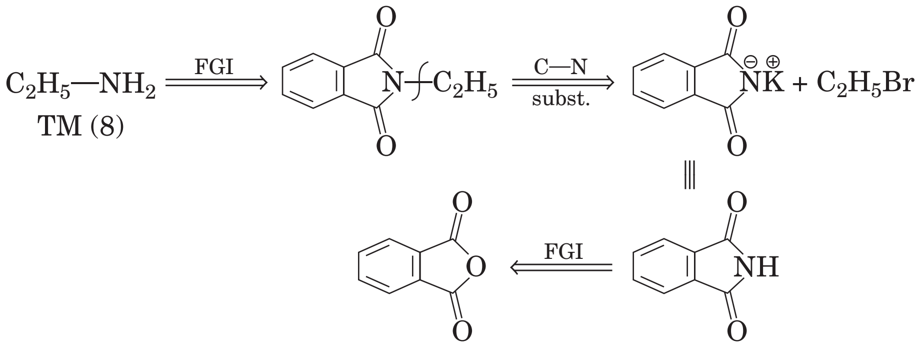
$$\underset{\text{TM (7)}}{C_2H_5\text{—}NH_2} \xRightarrow[\text{reduction}]{\text{FGI}} C_2H_5 \nmid N_3 \xRightarrow[\text{subst.}]{\text{C—N}} C_2H_5Br + N_3^{\ominus}$$

   Synthesis

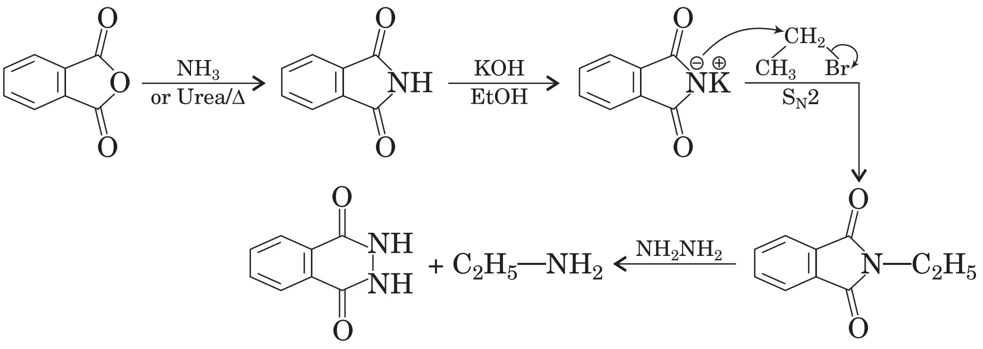
$$CH_3CH_2\text{—}Br \xrightarrow[S_N2]{NaN_3} CH_3CH_2\text{—}N_3 \xrightarrow[\text{or } H_2\text{, cat.}]{LiAlH_4} \text{TM (7)}$$

6. Although sodamide ($NaNH_2$) is commercially available, $NH_2^{\ominus}$ is very basic and therefore, takes up a proton, i.e., causes an elimination reaction, instead of displacing a halide ion by S_N2. The stable potassium salt of phthalimide (obtained from phthatic anhydride) can act as a reagent for $NH_2^{\ominus}$. The anion can react only once with the alkyl halide (S_N2) forming the substituted phthalimide which can be cleaved smoothly by hydrazine to produce the 1° amine. For example:

   Retrosynthetic analysis



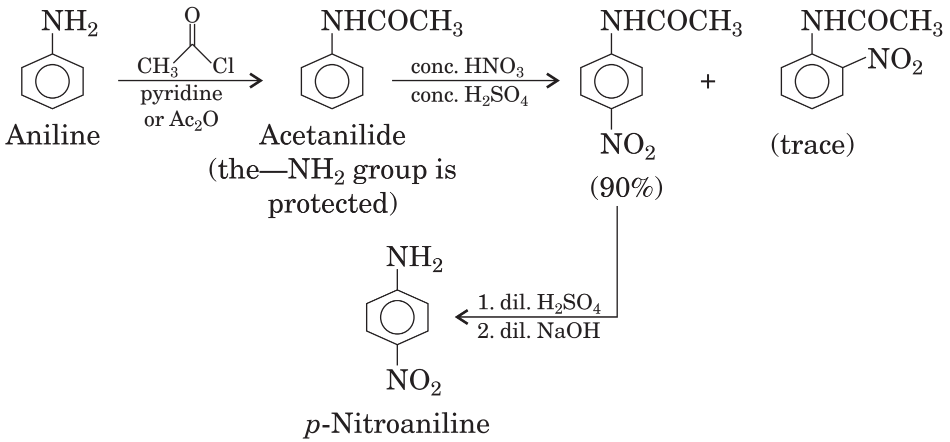
   Synthesis



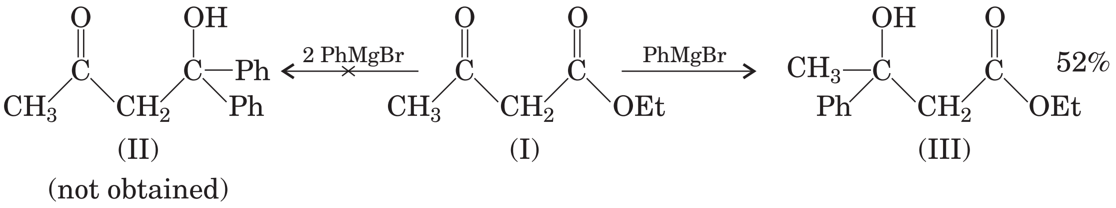
3.1.12 Protection-Deprotection Strategy (Alcohols, Amines, Carbonyl Compounds, Carboxylic Acids)

During synthesis of compounds, it is frequently necessary to carry out a transformation at one functional group while another reactive functional group remains unchanged. Two techniques are generally used to achieve this purpose. These are as follows (i) careful choice of a selective reagent and/or reaction conditions and (ii) temporary modification of the functional group at which the reaction is not desirable in such a manner that it remains unaffected during the reaction at the other functional group and may then be easily brought back to its original form. The group modifying the functional group is known as the *protecting group*. For example:

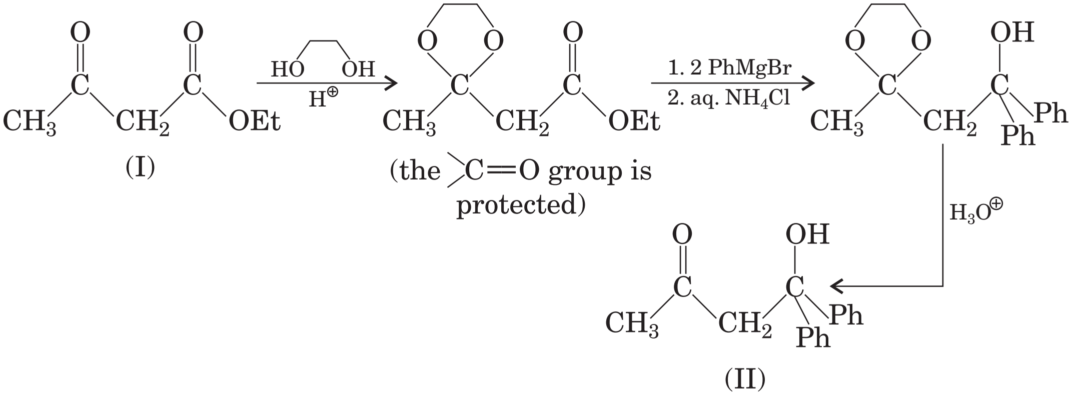
(i) If we want to carry out a nitration reaction on aniline to get *p*-nitroaniline, we cannot carry out the reaction directly on aniline and this is because the reaction leads to the formation of undesirable products owing to the powerful activating effect of and coordination of a proton to the $—\ddot{N}H_2$ group. Therefore, it requires to protect the amino group before nitration. When the nitration reaction is completed, the $–NH_2$ group is deprotected. In this nitration reaction, the amino group is protected by converting it to an amide by acetylation and deprotected by hydrolyzing *p*-nitroacetanilide to yield the desired *p*-nitroaniline.



(ii) The β-ketoester (I) cannot be converted to the β-hydroxy-ketone (II) by allowing it to react with phenylmagnesium bromide and this is because PhMgBr reacts with the more reactive $\left(\rangle C{=}O\right)$ group rather than the less reactive $–CO_2Et$ group to yield the β-hydroxyester (III).



The desired alcohol (II) can, however, be prepared by protecting the ($>$C=O) group as an acetal, i.e., an acetal (dioxolane) protecting group is to be used in this case.



The first step puts the protecting on to the more reactive (electrophilic) ketone carbonyl, making it no longer reactive towards nucleophilic addition. In the next step, Grignard adds to the ester group, and finally the keto group is deprotected by acid-catalyzed hydrolysis of the acetal. It is to be noted that an acetal is an ideal choice here because acetals are stable to base (the conditions of the Grignard reaction involving the strong base $R^{\ominus}$), but are readily cleaved by aqueous acid.

An ideal protecting group must have the following characteristics:

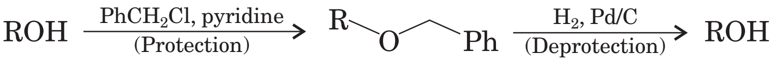
(i) it should be introduced under mild conditions and the yield of the product should be high;

(ii) it should be stable under the reaction conditions required for carrying out transformation at the other functional group; and

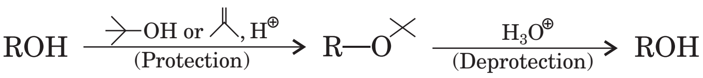
(iii) it should be removed easily under mild conditions.

1. Protection and deprotection of alcohols Some important protecting groups for alcohols including 1,2- and 1,3-diols are discussed below:

(a) Formation of ethers Certain ethers, which are easily cleaved under mild conditions, are commonly used as protecting groups for alcohols, e.g. benzyl ethers which are converted to alcohols under neutral conditions by catalytic hydrogenolysis and *t*-butyl ethers which are readily removed by treatment with HCl, HBr or CF_3COOH.



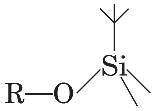
Benzyl ether (ROBn)
stable to base, mild
acid, oxidation, and
reduction



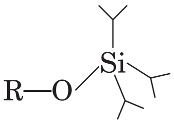
It is triphenylmethyl ('trityl') ether which is the most important for the protection of 1° alcoholic group. Only 1° alcohols react at useful rate with trityl chloride in pyridine and so, selective protection of primary hydroxyl group is possible. This is an S_N1 reaction with an enormous electrophile – so big that goes on primary alcohols only. The trityl group offers good resistance to bases but is easily removed by treatment of acids like CF_3CO_2H or HCO_2H.

$$RCH_2OH \xrightarrow[\text{(Protection)}]{Ph_3CCl,\ \text{pyridine}} RCH_2OCPh_3 \xrightarrow[\text{(Deprotection)}]{CF_3CO_2H\ \text{or}\ HCO_2H} RCH_2OH$$

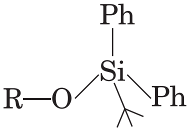
(b) Formation of silyl ethers The ethers formed by treatment of alcohols with trialkyl silyl halides and base is specially important in protection of alcohols in protective group chemistry. Trimethylsilyl ethers are rather unstable and are easily cleaved by mild acids and bases. However, when the methyl groups are replaced by more bulky groups, very stable compounds are produced that are highly resistant to strongly acidic and basic conditions but are readily removed by treatment with fluoride ion. A convenient source of $F^{\ominus}$ ion for this purpose is *tetra*-*n*-butylammonium fluoride (Bu_4NF or TBAF). Examples of some bulky trialkylsilyl protecting groups are given below:



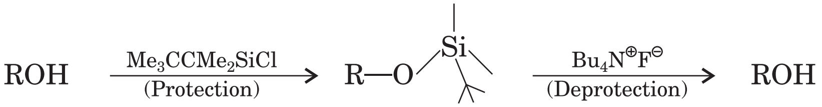
t-Butyldimethylsilyl ether
(R—OTBDMS)



Triisopropylsilyl ether
(R—OTIPS)

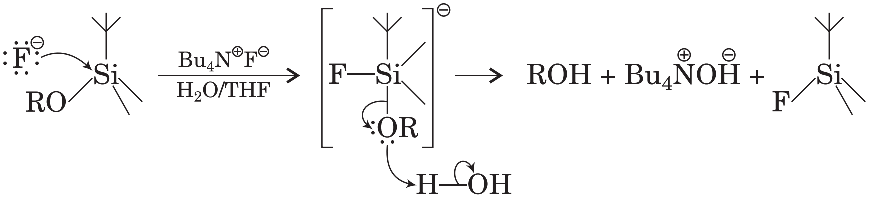


t-Butyldiphenylsilyl ether
(R—OTBDPS)



Protected alcohol

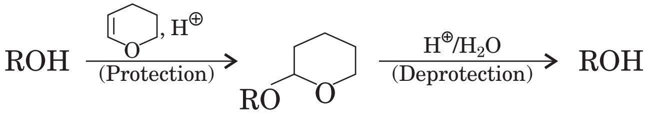
Mechanism of deprotection:



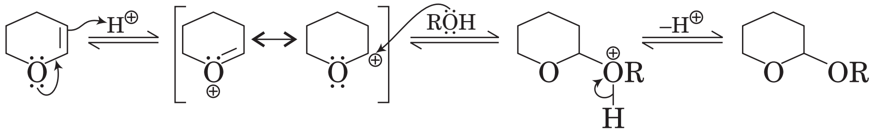
$F^{\ominus}$ attacks a vacant 3*d* orbital of silicon, giving an intermediate pentacoordinated anion. The intermediate then dissociates to gives an alcohol.

(c) Formation of acetals Acetals not only serve as useful protecting groups for aldehydes and ketones but they also find widespread use in the protection of alcohols. The commonly used acetals include *tetra*hydropyranyl (THP) derivatives (obtained when an alcohol is allowed to react with dihydropyran in the presence of acid catalyst), methoxyethoxymethyl (MEM) derivative (obtained when an alcohol is allowed to react with methoxyethoxymethyl chloride under basic conditions) and methoxymethyl (MOM) derivative (prepared by the reaction of an alcohol with methoxymethyl chloride under basic condtions). While the THP and MOM groups are removed by treating with dilute acid, the MEM group is stable under these conditions but is removed by a Lewis acid ($TiCl_4$ or $ZnBr_2$).

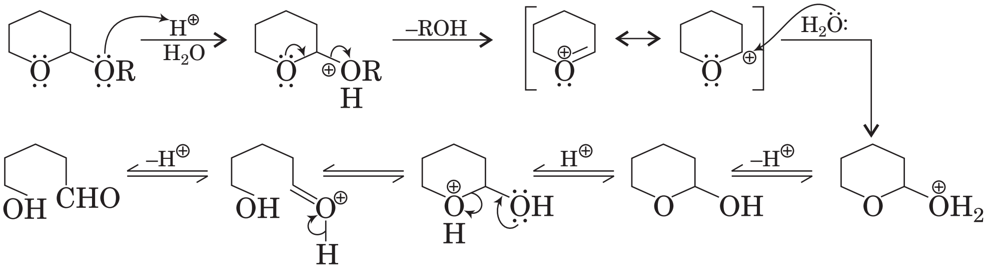
(i)



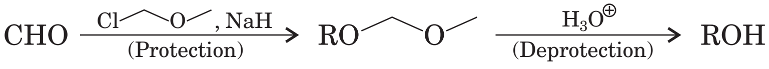
Mechanism of protection:



Mechanism of deprotection:

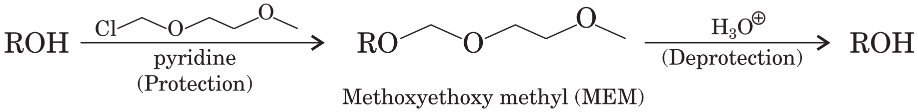


(ii)



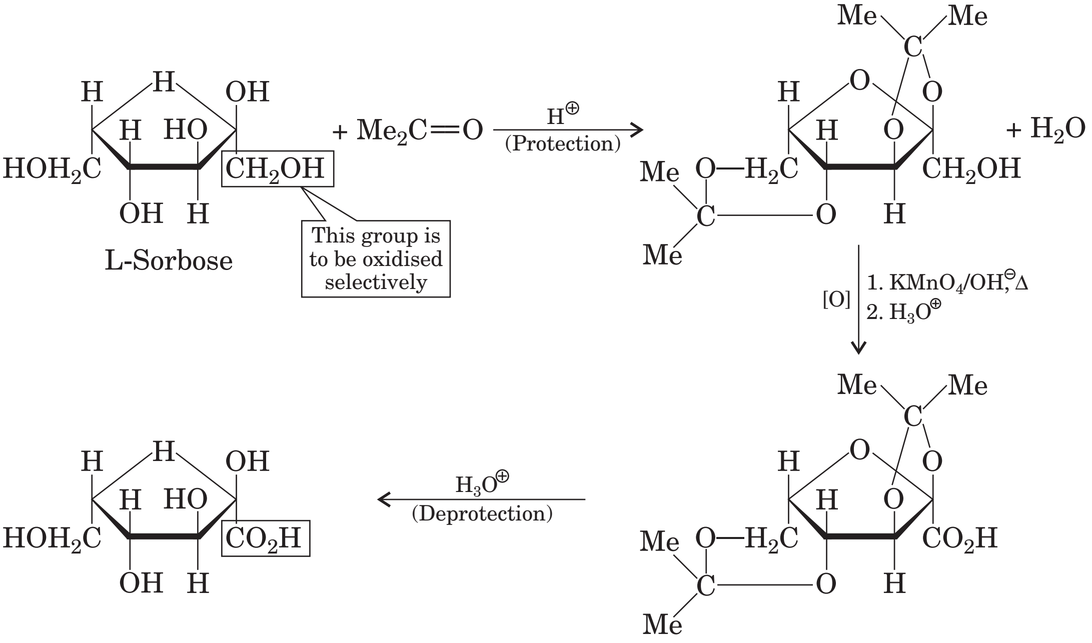
Methoxymethyl (MOM)
ether: stable to
oxidation, reduction
and base.

(iii)



Methoxyethoxy methyl (MEM)
ether: stable to oxidation,
reduction and base

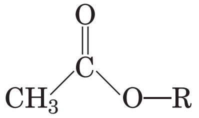
Protecting groups for 1,2- and 1,3-diols *Cis*-1,2,-diols and *cis*- and *trans*-1,3-diols can be well protected as cyclic acetals (e.g., 1,3-dioxolanes or 1,3-dioxanes) or cyclic orthoesters that can be smoothly cleaved by acidic hydrolysis, or as cyclic esters (e.g., carbonates and boronates) that are cleaved by basic hydrolysis. For example, a key step in a synthesis of vitamin C involves selective oxidation of a primary alcoholic group of L-sorbose. To achieve this, all but one of the hydroxyl groups are protected by conversion to a double isopropylidene acetal.



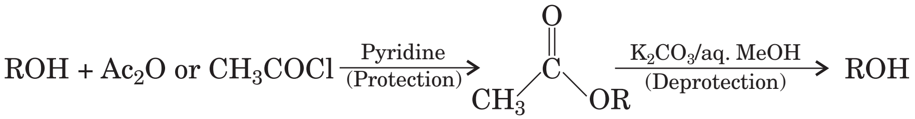
Benzaldehyde, acetone and cyclohexanone are the common carbonyl compounds used for the preparation of acetals. Triethyl or trimethyl orthoformate in the presence of acid catalyst is used to prepare cyclic ortho esters and phosgene in the presence of a base is used to prepare cyclic carbonates.

(d) Formation of esters Esterification is the final important way to protect an alcohol. The groups are easily introduced by allowing alcohols to react with the appropriate acyl chloride or anhydride in the presence of base and are stable under a variety of conditions. They can be removed by hydrolysis in basic medium. The most useful esters for protecting alcohols are given below:

(i) **Acetate esters:**

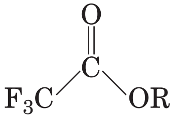


$$CH_3C(=O)O{-}R$$

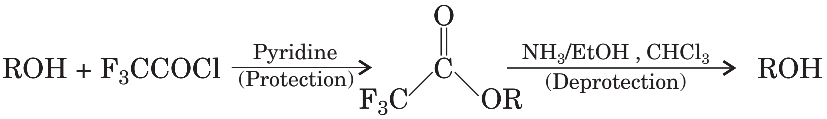


$$ROH + Ac_2O \text{ or } CH_3COCl \xrightarrow[\text{(Protection)}]{\text{Pyridine}} CH_3C(=O)OR \xrightarrow[\text{(Deprotection)}]{K_2CO_3/\text{aq. MeOH}} ROH$$

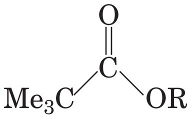
(ii) **Trifluoroacetate esters:**

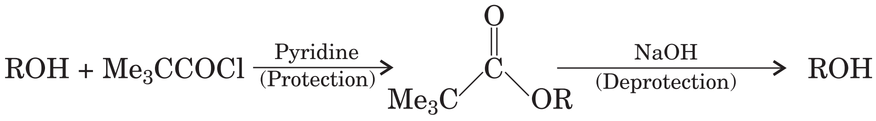


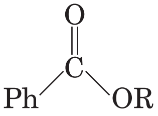
$$F_3CC(=O)OR$$

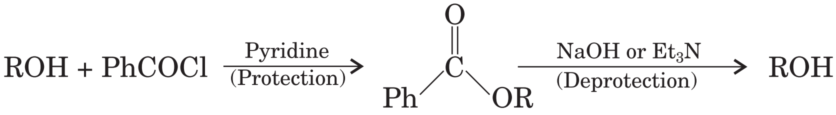


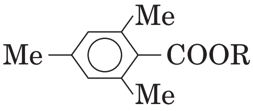
$$ROH + F_3CCOCl \xrightarrow[\text{(Protection)}]{\text{Pyridine}} F_3CC(=O)OR \xrightarrow[\text{(Deprotection)}]{NH_3/EtOH\text{ , }CHCl_3} ROH$$

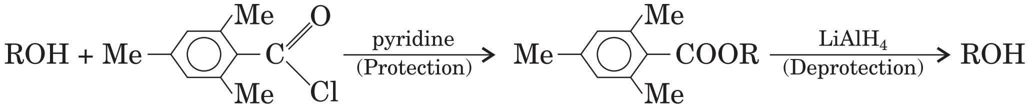
(iii) **Pivaloate esters:** 



(iv) **Benzoate esters:** 



(v) **2,4,6-Trimethylbenzoate esters:** 

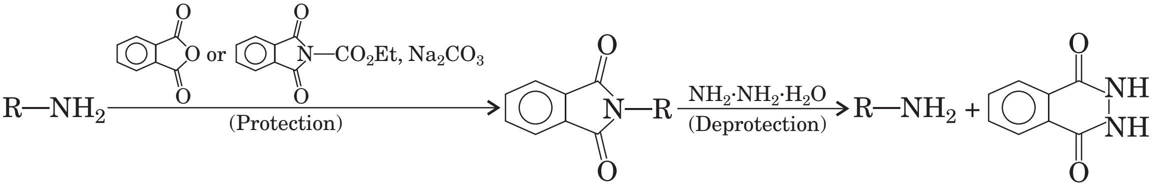


2. Protection and deprotection of amines Because amines compete so effectively for electrophiles, it can be very difficult to handle molecules with free amino group, both from the point of view of reactivity and ease of purification. Therefore, a good plan is to keep the amine in a protected form to avoid unwanted reactions. It can be done by quarternisation or by bringing the lone pair into conjugation with a π-system. The methods generally employed for protection and deprotection of amines are as follows:

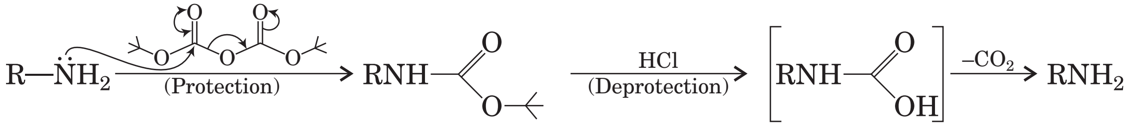
(a) *N*-alkylation This is perhaps the simplest approach for protection of amines. The most commonly used groups are *N*-benzyl, triphenylmethyl (trityl) and allyl, which are all introduced by reaction with appropriate halide in the presence of a base. Debenzylation can be effected with Na/NH_3(l) or by catalytic transfer hydrogenation using Pd—C and HCOOH as the hydrogen source. Removal of *N*-trityl group can be achieved with sodium in liquid NH_3, acid hydrolysis or catalytic hydrogenation and the *N*-allyl group can be removed by rhodium catalysed isomerization to the enamine followed by acid hydrolysis.

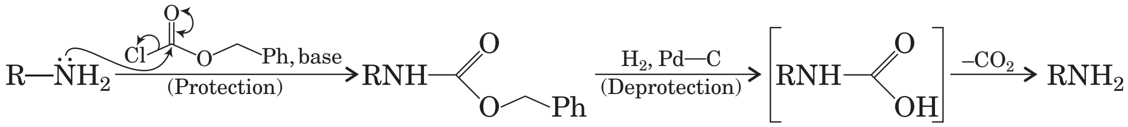
(b) *N*-acylation An amine can be converted to an amide by acylation with a suitable acyl chloride or anhydride. The most commonly used groups of this type are *N*-acetyl, *N*-trifluroacetyl, and *N*-benzoyl; these effectively suppress the basic character of the amine function and reduce the nucelophilicity of nitrogen. Among these three groups, *N*-trifluoroacetyl is removed most easily, for example by treatment with sodium bicarbonate solution. Removal of the acetyl group requires treatment with HCl or hydrazine, while an

N-benzoyl group is very difficult to remove and it requires treatment with moderately concentrated HCl or HBr in acetic acid. When protection of both amino hydrogens of a primary amine is required, a very robust protecting group is the phthaloyl derivative. This can be introduced by heating a primary amine with phthalic anhydride or by an exchange reaction with *N*-ethoxycarbonyl phthalimide and sodium carbonate. The group can be removed simply by treatment with hydrazine hydrate ($NH_2NH_2 \cdot H_2O$).

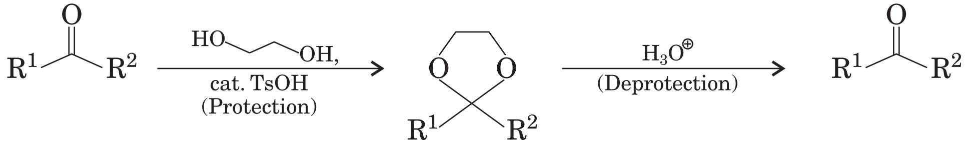


(c) Formation of carbamates Carbamate protecting groups are by far the most commonly used since they offer effective protection under a wide variety of conditions and carry less risk of racemization than the acyl group. The groups can be smoothly introduced by treating with the appropriate chloroformate under basic conditions. An exception is the *t*-butoxycarbonyl or Boc group (CO_2CMC_3) for which either di-*t*-butyl dicarbonate or *t*-butyl azidoformate must be used. Carbamic acids $\left(\rangle N—CO_2H\right)$ being unstable decarboxylate spontaneously to regenerate the amine. Therefore, the deprotection methods simply require conversion of the OR group into the OH group. Benzyloxycarbonyl or Cbz group (CO_2CH_2Ph) and the Boc group are readily removed by catalytic hydrogenation and hydrochloric acid, respectively.

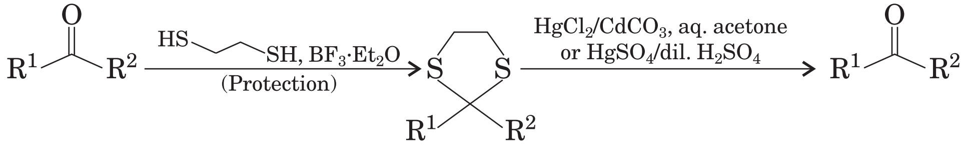




3. Protection and deprotection of aldehydes and ketones During synthetic processes, the protection of a carbonyl group is usually required to prevent attack by various reagents such as strong or moderately strong nucleophiles including organometallic reagents, acidic or basic catalysts, hydride reducing agents and some oxidizing agents. Since the reactivity order of the carbonyl group is aldehyde (aliphatic > aromatic) > acyclic ketones and cyclohexanones > cyclopentanones > α,β-unsaturated ketones >> aromatic ketones, it may be possible to protect a more reactive carbonyl group selectively in the presence of a less reactive one. The acyclic or cyclic acetals and acyclic or cyclic thioacetals are the most useful protecting groups for carbonyl compounds. The protecting group is to be introduced by treating the carbonyl compound with an alcohol or a diol in the presence of acid catalyst or with a thiol or dithiol and boron trifluoride etherate. Cyclic and acyclic acetals are stable to aqueous and monaqueous bases, to nucleophiles including organometallic reagents, and to hydride donors. The carbonyl group can be regenerated from acetals by acid hydrolysis and from thioacetals by $HgCl_2/CdCO_3$ or by refluxing an aqueous alcoholic solution containing $HgSO_4$ and H_2SO_4.



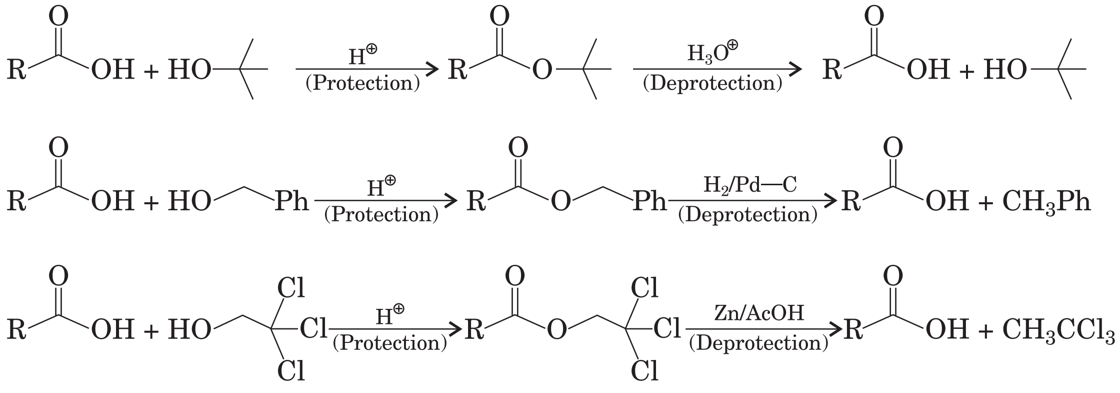
Acetal



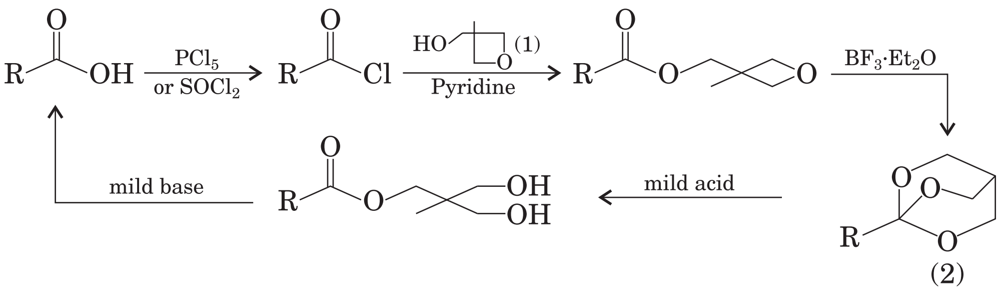
Thioacetal

4. Protection and deprotection of carboxylic acids The useful method employed for protection and deprotection of carboxyl group are as follows:

(a) Formation of esters The hydroxyl group of a carboxylic acid can be protected in the same way as that of an alcohol by alkylation which results in formation of an ester. Esterification can be readily achieved by treatment with the appropriate alcohol and an acid catalyst although milder conditions involving diazomethane (CH_2N_2) to form methyl esters can also be used. Simple alkyl esters (methyl or ethyl) generally serve the purpose. However, if it requires to protect against nucleophilic attack by organometallic reagents or the substrate is very much complex that ester cleavage has to be unambiguous and then special esters will be required. *tert*-Butyl and benzyl esters are the most commonly used special esters. The *tert*-butyl group offers moderate protection against nucleophilic attack and is readily removed by acidic hydrolysis ($A_{AL}1$ mechanism involving *tert*-butyl cation). The benzyl group is usually removed by hydrogenation. The MOM, MTM, MEM and various silyl esters have also been used. One group of particular value is the 2,2,2-trichloroethyl ester, $RCO_2CH_2CCl_3$, which is removed under mild conditions by reduction with zinc in ACOH.

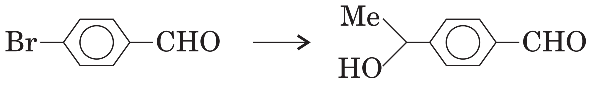


(b) Formation of *ortho* ester While conventional esters protect the COOH group against deprotection with common bases, they do not offer any protection against nucleophilic attack by organometallic reagents or against enolate formation with strong bases. An important way of achieving this is to form the bicyclic ester, normally referred to as OBO ester, by treating the acid chloride with the oxetane alcohol (1) to give the simple ester and converting this into ortho ester (2) by treatment with BF_3-etherate. Although the OBO ester is stable towards organolithium and Grignard reagents, it can be easily removed by treatment with mild acid followed by mild base.

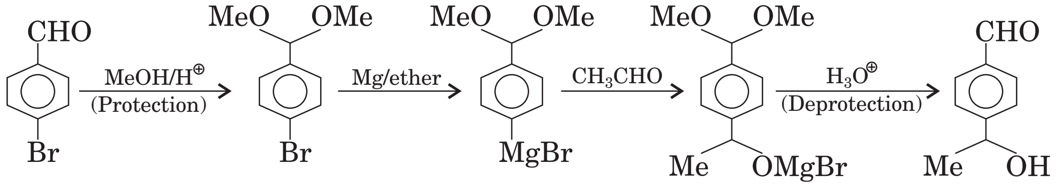


Some conversions involving use of protective groups

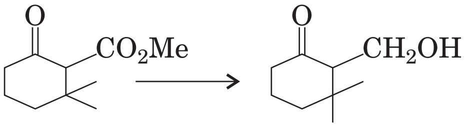
(i)



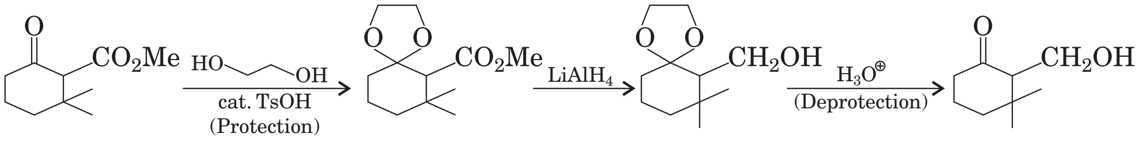
The —CH(OH)Me group can be introduced *para* to —CHO simply by a Grignard reaction. But the Grignard reagent will react readily with an aldehyde, i.e., with itself. For this reason, the —CHO group must be protected.



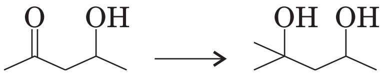
(ii)



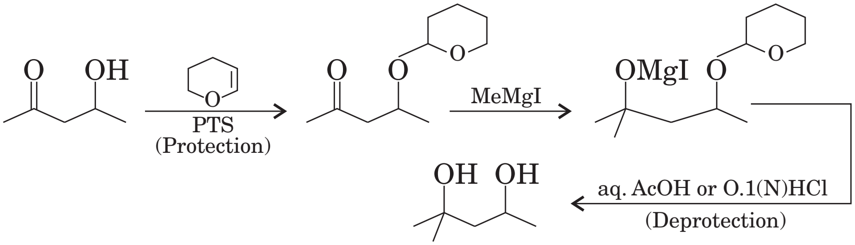
Since the $>C=O$ group is much more readily reduced than ester group, it is to be protected.



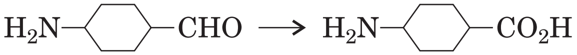
(iii)



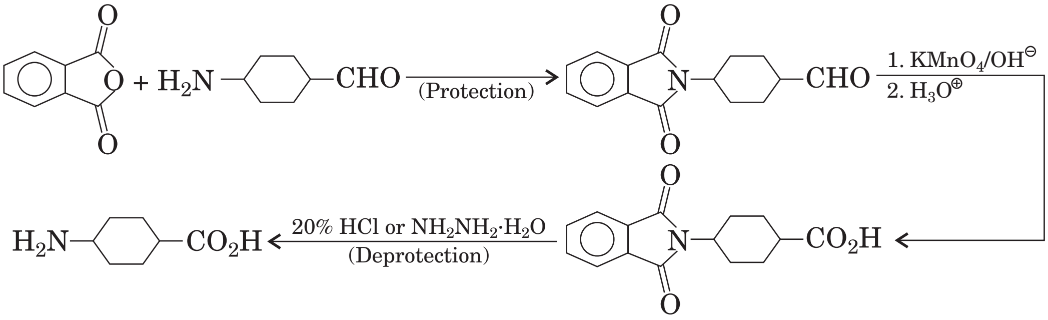
Since MeMgI reacts readily with the active hydrogen containing –OH group, it is to be protected.



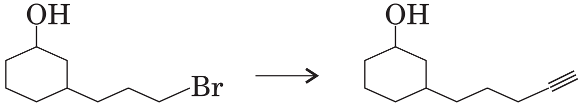
(iv)



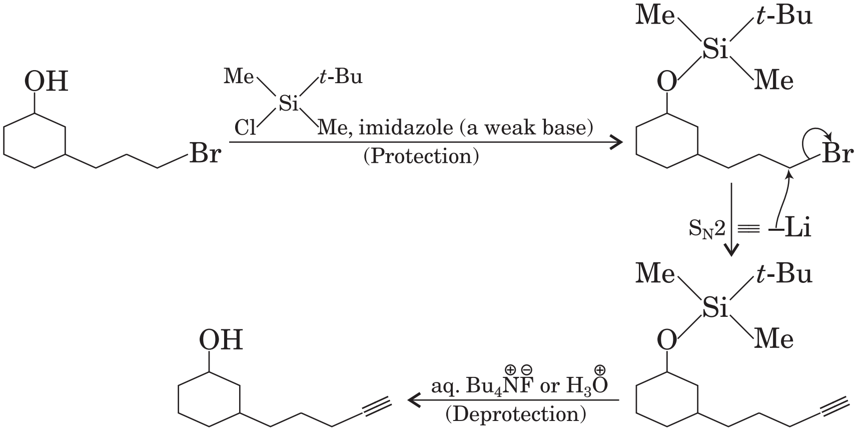
Before oxidizing the –CHO group, the $-NH_2$ group is to be protected against oxidation.



(v)

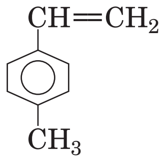


Alkylation of the acetylide ion with the bromo compound is not possible because the anion acts as a base and readily deprotonate the hydroxyl group. Because of this, the hydroxyl group is to be protected.

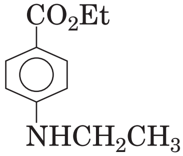


SOLVED PROBLEMS

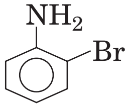
1. **Using disconnection approach, outline the synthesis of each of the following benzenoid target molecules:**

(a)


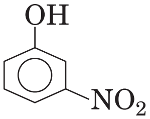
TM (1)

(b)


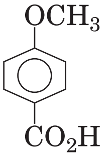
TM (2)

(c)


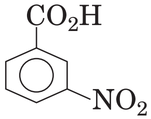
TM (3)

(d)


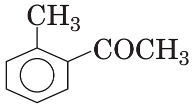
TM (4)

(e)


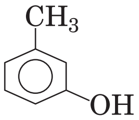
TM (5)

(f)


TM (6)

(g)


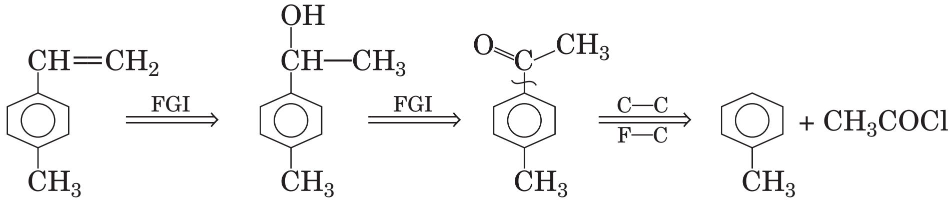
TM (7)

(h)


TM (8)

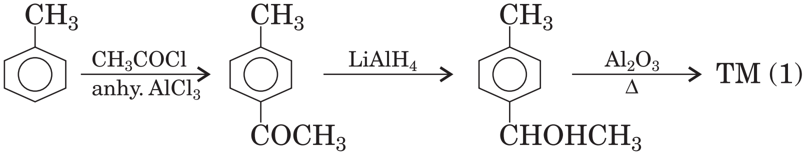
Solution

(a) *Retrosynthetic analysis*

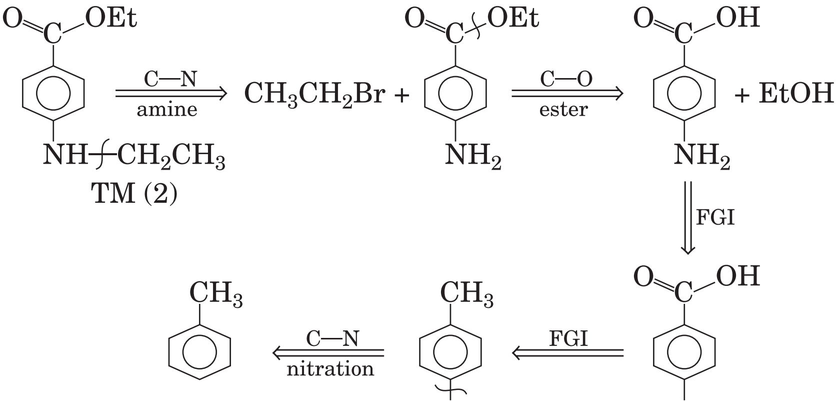


TM (1)   Toluene

Synthesis



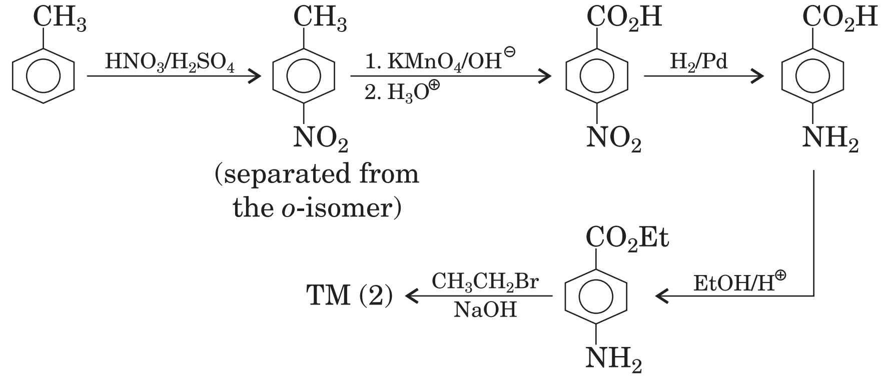
(b) *Retrosynthetic analysis*



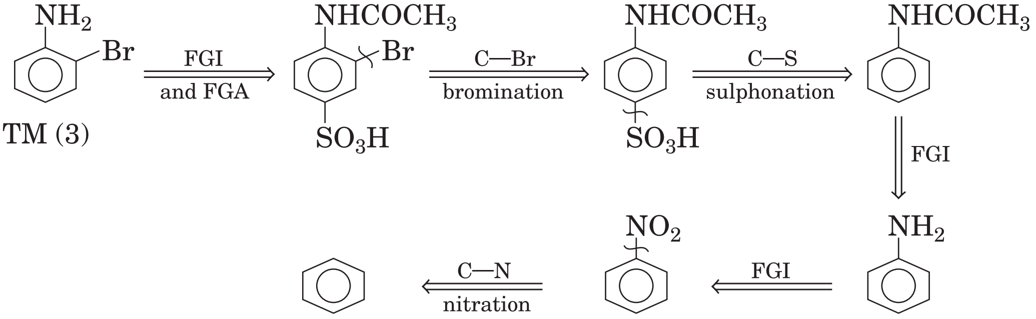
TM (2)

Toluene

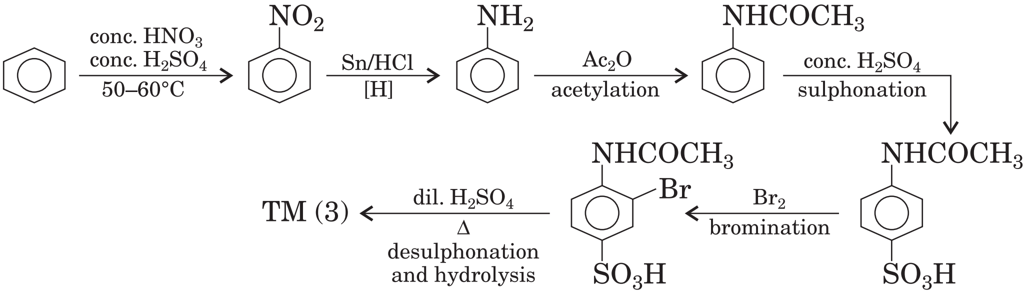
Synthesis



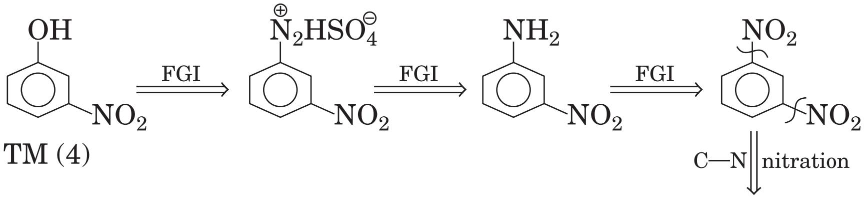
(c) *Retrosynthetic analysis*



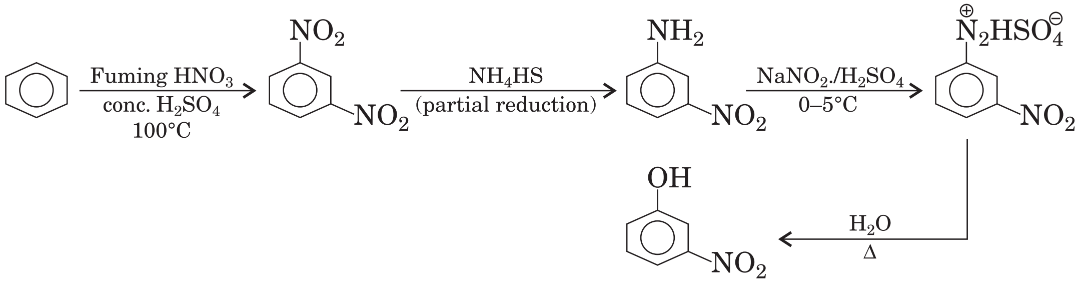
Synthesis



(d) *Retrosynthetic analysis*

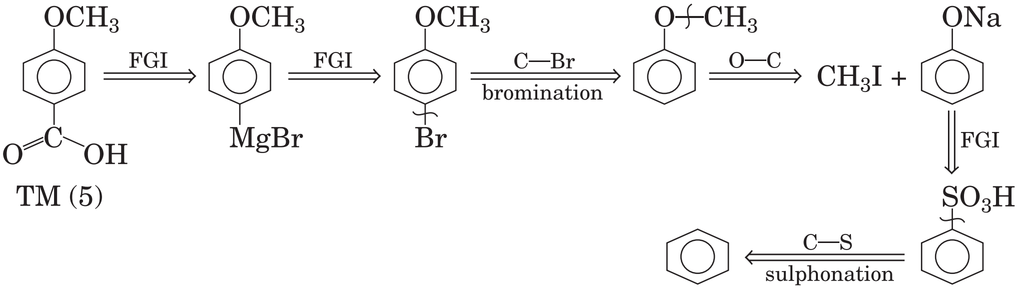


Synthesis

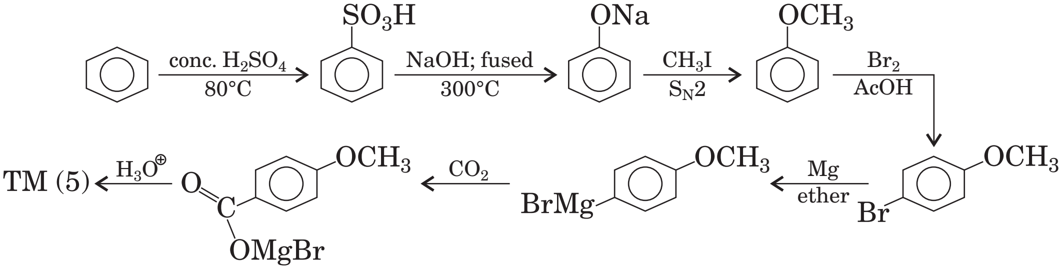


m-Nitrophenol

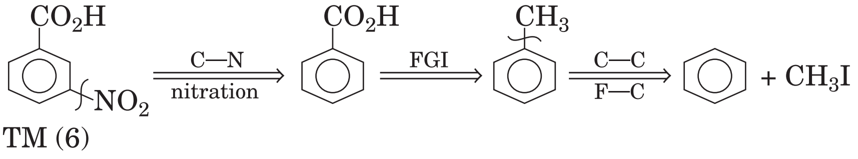
(e) *Retrosynthetic analysis*



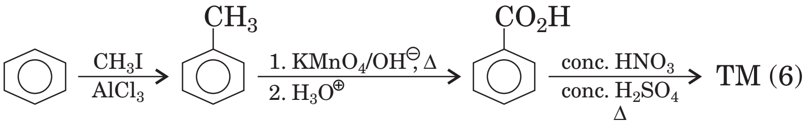
Synthesis



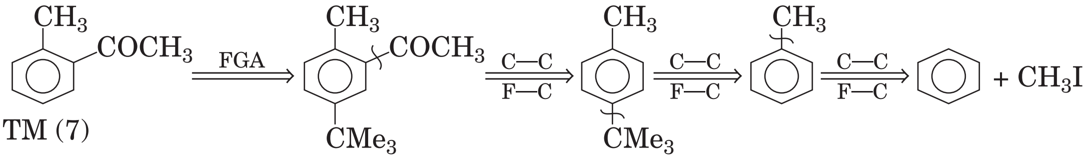
(f) *Retrosynthetic analysis*



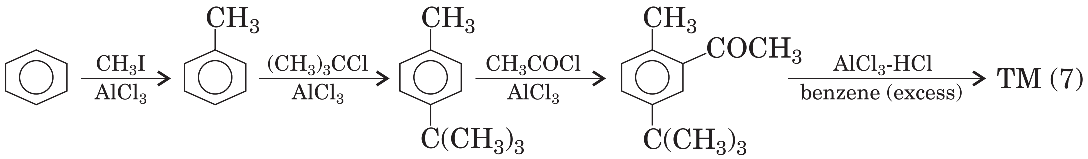
Synthesis



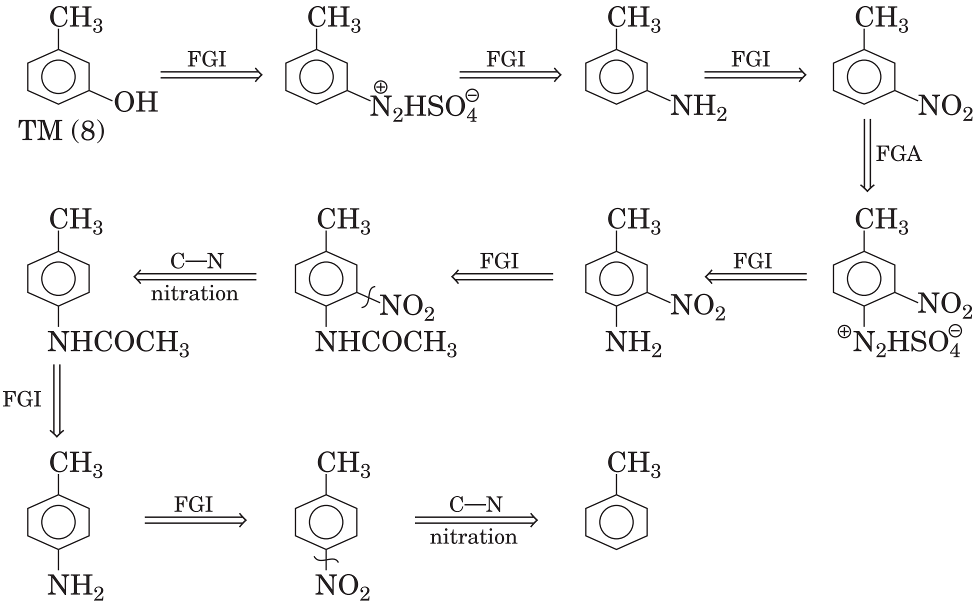
(g) *Retrosynthetic analysis*



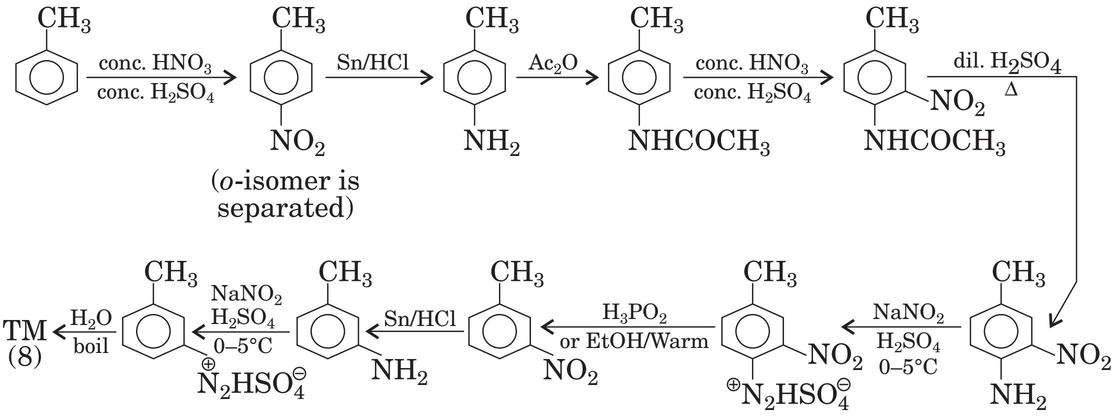
Synthesis



(h) *Retrosynthetic analysis*

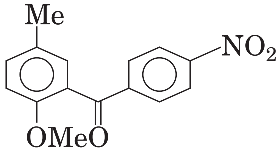


Synthesis



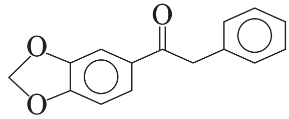
2. Predict the two possible retrosynthetic pathways for each of the following two ketones and comment on the pathway which is expected to be the better one in each case.

(a)



TM (9)

(b)

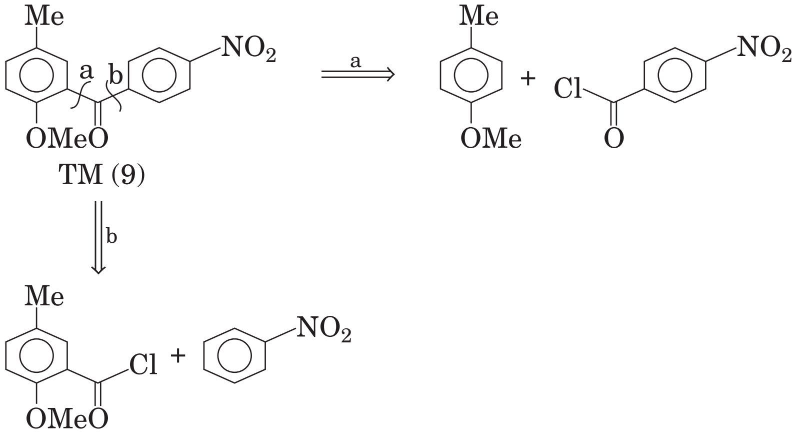


TM (10)

Solution

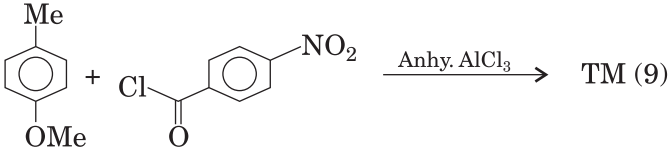
(a) In principle, any bond next to an aromatic ring is to be disconnected. Therefore, the two possible disconnections are as follows:

Retrosynthetic analysis

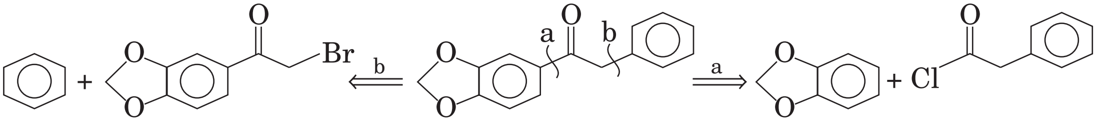


The disconnection (b) is not at all effective because the nitro group is *m*-directing and nitrobenzene does not undergo the Friedel–Crafts reaction because the ring is considerably deactivated. On the other hand, the disconnection (a) is a very good one because it gives an activated ring (both –Me and –OMe are electron-releasing) which undergoes the Friedel–Crafts reaction smoothly. Now, the –OMe group is a more powerfully *ortho*-directing group than –Me and so, it places the acyl group *ortho* to it predominantly.

Synthesis



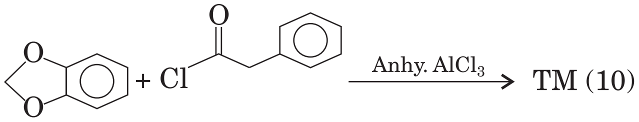
(b) *Retrosynthetic analysis*



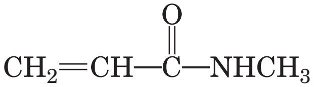
An alkyl halide TM (10) An activated benzene ring

Between these two possible disconnections (a) is relatively better as it gives an acyl rather than an alkyl halide (which is difficult to prepare from the corresponding ketone because the activated ring, due to two directly attached oxygens, may also undergo bromination) and an activated benzene ring. Hence, the disconnection (a) is better for the synthesis of this target molecule.

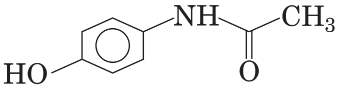
Synthesis



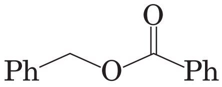
3. Outline the retrosynthetic analysis (involving one-group C—X disconnection) and the designed synthesis of the following target molecules:

(a)

$CH_2=CH-\overset{O}{\overset{\|}{C}}-NHCH_3$

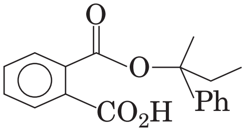
TM (11)

(b)


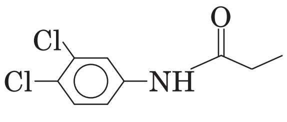
TM (12)

(c)


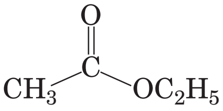
TM (13)

(d)


TM (14)

(e)


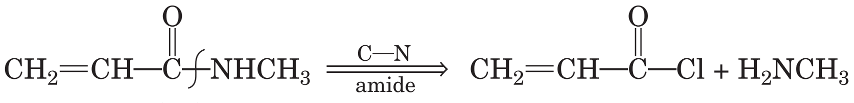
TM (15)

(f)

$CH_3-\overset{O}{\overset{\|}{C}}-OC_2H_5$

TM (16)

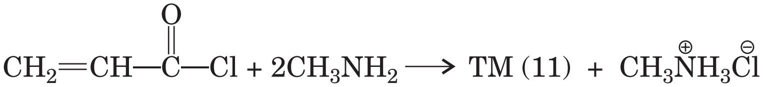
Solution

(a) *Retrosynthetic analysis*


$$CH_2=CH-\overset{O}{\overset{\|}{C}}\wr NHCH_3 \xRightarrow[\text{amide}]{C-N} CH_2=CH-\overset{O}{\overset{\|}{C}}-Cl + H_2NCH_3$$

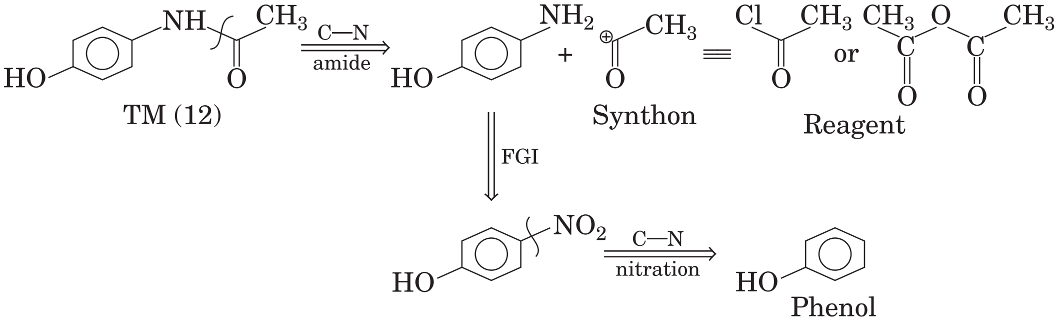
TM (11)

Synthesis



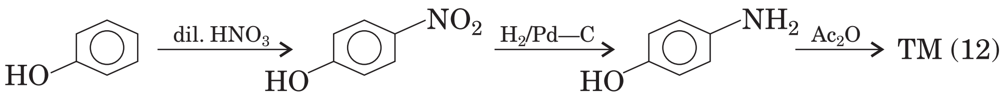
$$CH_2{=}CH{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}Cl + 2CH_3NH_2 \longrightarrow \text{TM (11)} + CH_3\overset{\oplus}{N}H_3\overset{\ominus}{Cl}$$

(b)



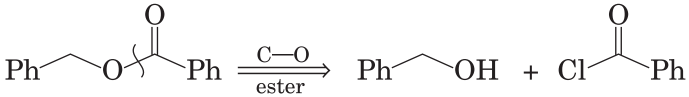
The reagent *p*-aminophenol has two reactive groups; however, amines are far more nucleophilic than phenols. Thus, the formation of *O*-acetylated product is largely avoided during the nucleophilic acyl substitution involving either of these reactive groups.

Synthesis



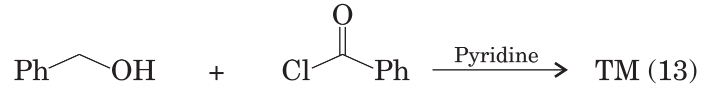
(the *o*-isomer is
separated by
steam distillation)

(c) *Retrosynthetic analysis*



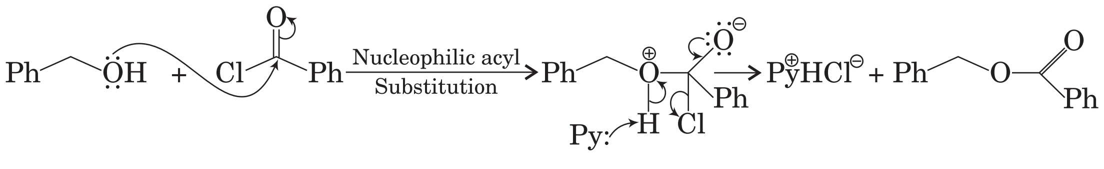
TM (13)

Synthesis



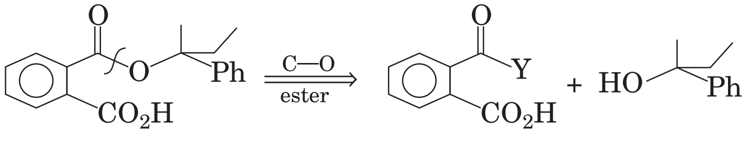
Benzyl alcohol   Benzoyl chloride

Mechanism:



Pyridine may also react with the acyl chloride to form an acyl pyridinium ion, an intermediate that is even more reactive towards the nucleophile than the acylchloride.

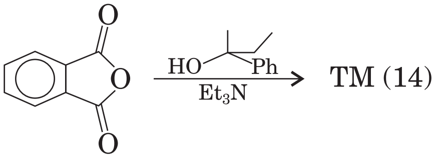
(d) *Retrosynthetic analysis*



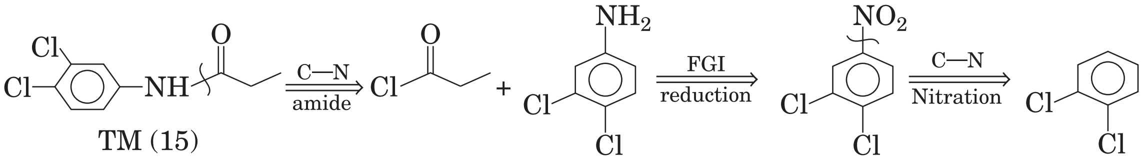
TM (14)

Synthesis

Phthalic anhydride (a very cheap reagent) is the best acid derivative which is to be used in this synthesis.

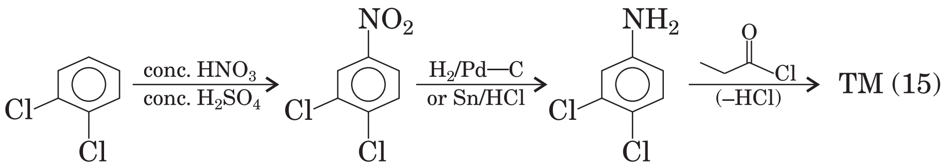


(e) *Retrosynthetic analysis*

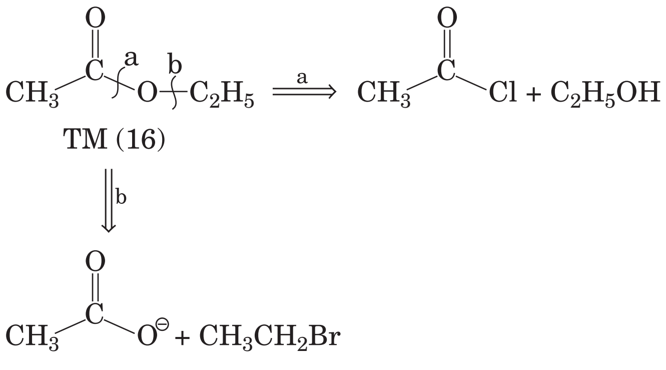


TM (15)

Synthesis

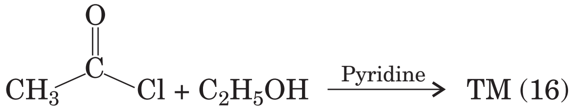


(f) *Retrosynthetic analysis*



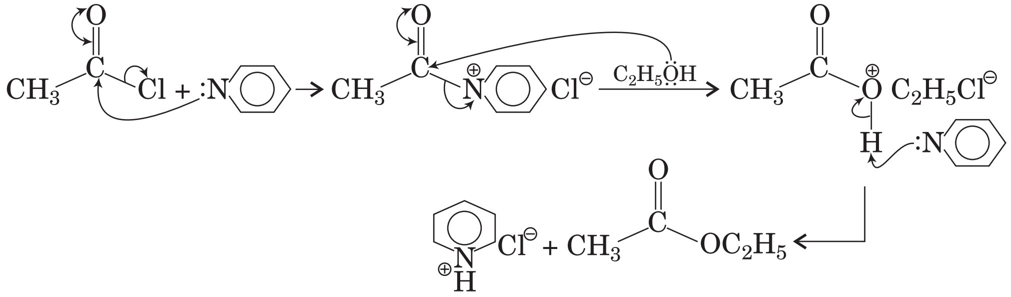
The disconnection (b) between the alkyl group and the heteroatom would need an S_N2 reaction between the carboxylate anion ($CH_3COO^{\ominus}$) and an alkyl halide (CH_3CH_2Br). Reactions at the carbonyl group (nucleophilic acyl substitution) are much more facile than S_N2 reactions, and therefore, the disconnection (a) is preferred.

Synthesis



$$CH_3C(=O)Cl + C_2H_5OH \xrightarrow{\text{Pyridine}} \text{TM (16)}$$

Mechanism:



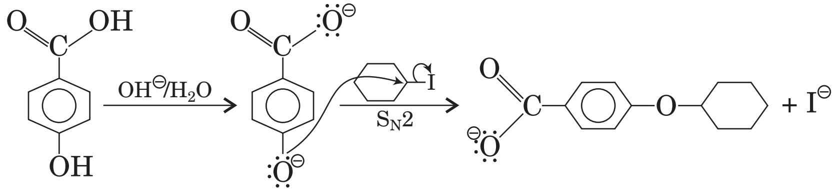
[It is to be noted that an S_N2 reaction may be highly facile and very fast if the substrate possesses special structure that makes the T.S. much more stable (e.g., CH_3COCH_2Cl undergoes S_N2 reaction 10^5 times faster than CH_3Cl).]

4. **What is called a chemoselective reaction? Comment on the term chemoselectivity and give some guidelines for solving the problem of chemoselectivity.**

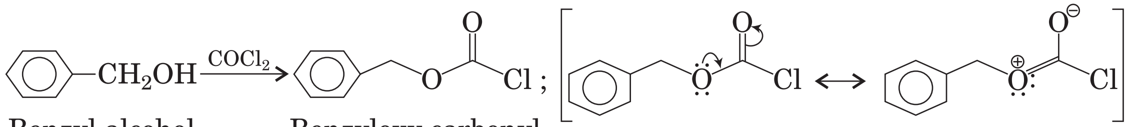
Solution A chemoselective reaction is one in which the reagent reacts specifically with one functional group within a molecule leaving other potentially reactive functional group(s) unchanged.

Chemoselectivity is a term coined for the preference of a reagent to react with one functional group leaving other functional group(s) unaffected. The problem of chemoselectivity arises when a substrate contains two or more reactive groups and one of them requires modification. The guidelines for solving this problem are as follows:

1. When a substrate containing two functional groups of unequal reactivity is allowed to react with a reagent, the more reactive one reacts alone to give the product. For example, in alkaline solution (pH > 10), both of the two groups of *p*-hydroxybenzoic acid undergo ionization. When the salt is allowed to react with an alkyl halide, an ether instead of an ester is formed and this is because the phenoxide ion is relatively more reactive than the carboxylate ion.



2. The starting compound and the first product will compete for the reagent when one functional group can react twice. If the first product is less reactive than the starting compound, the reaction can be successfully utilized to solve the purpose. For example, benzyl alcohol must react with phosgene once only to yield benzyloxycarbonyl chloride, $PhCH_2OCOCl$ (used to protect the amino group in peptide synthesis). This succeeds since the acid chloride is less reactive than the double acid chloride $COCl_2$, because of conjugation.



Benzyl alcohol

Benzyloxy carbonyl chloride or benzyl chloroformate

The positive character of the carboxyl carbon is reduced due to conjugation.

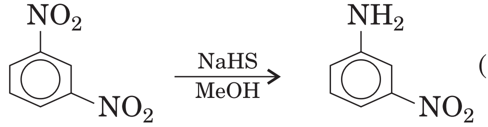
3. One of the two identical functional groups may react if one equivalent of the reagent is used. For example, monoalkylation of 1,3-propanediol can be effected in good yield by using one equivalent of metallic sodium in xylene.

$$HO(CH_2)_3OH \xrightarrow[\text{Xylene}]{\text{Na(1 eq.)}} HO(CH_2)_3\ddot{\underset{\cdot\cdot}{O}}{:}^{\ominus} \xrightarrow[S_N2]{CH_3CH_2Br} HO(CH_2)_3OCH_2CH_3$$

1,3-Propanediol 1-Ethoxy-3-hydroxypropane

4. One of the two identical groups may react if the product is less reactive than the starting material. For example:

(i)

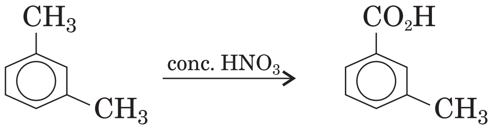


(Partial reduction)

m-Dinitrobenzene *m*-Nitroaniline

When *m*-dinitrobenzene is partially reduced, *m*-nitroaniline is obtained. Reduction involves electron take up by the substrate from the reducing agent. Due to presence of an electron-donating $-NH_2$ group, the reactivity of the product *m*-nitroaniline compared to the starting compound is decreased. For this reason, further reduction does not take place.

(ii)

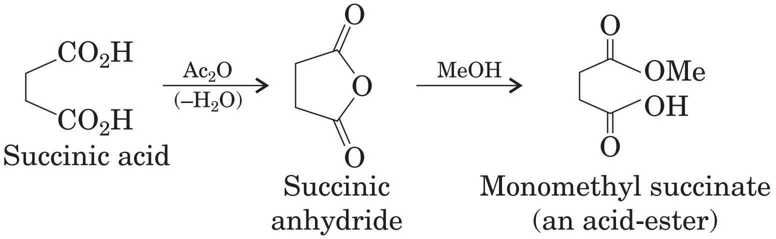


(Partial oxidation)

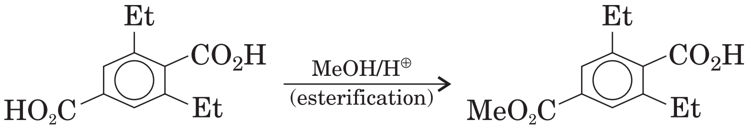
m-Xylene *m*-Toluic acid

m-Xylene undergoes partial oxidation to yield *m*-toluic acid. Oxidation involves removal of electrons from the substrate. Due to presence of an electron-attracting –COOH group, *m*-toluic acid is less reactive than *m*-xylene. As a consequence, further oxidation does not take place.

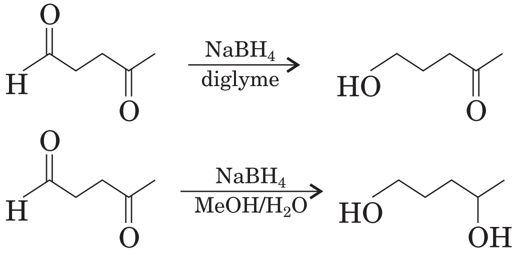
5. One of the two identical functional groups can be changed by a much reliable method in which a derivative is used which can react once only with the reagent. A cyclic anhydride is the most important example. One of the two –COOH groups of succinic acid can be esterified via its cyclic anhydride. Alcohols react with the anhydride to yield an acid-ester which is no longer reactive.



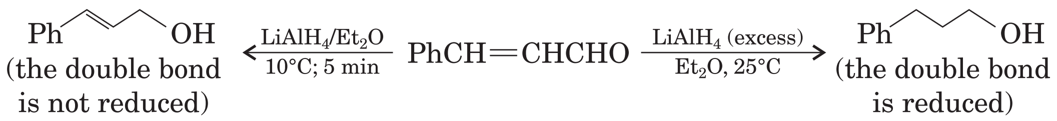
6. When the approach of the reagent to one of the two identical functional groups is sterically hindered, then the other functional group reacts preferentially. For example, in the following dicarboxylic acid, the –COOH group flanked by two ethyl groups does not undergo esterification because it is sterically congested.



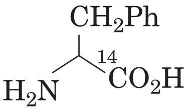
7. Solvent plays an important role to obtain the desired selectivity of a reaction. Sodium borohydride in diglyme, for example, reduces a –CHO group but fails to reduce a $\rangle C{=}O$ group. However, in aqueous methanolic medium, it reduces both the functional groups.

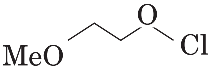


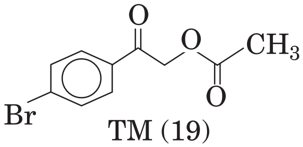
8. The conditions of the reaction (temperature and pressure), the amount of the reagent used and the reaction time are also important to obtain desired selectivity. For example:

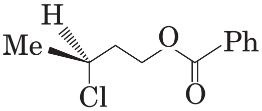


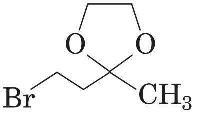
5. Outline the retrosynthetic analysis (involving two-group C—X disconnection) and the designed synthesis of the following target molecules:

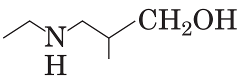
(a)

TM (17)

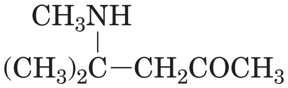
(b)

TM (18)

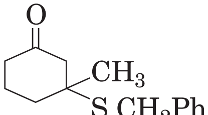
(c)

TM (19)

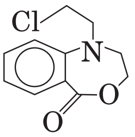
(d)

TM (20)

(e)

TM (21)

(f)

TM (22)

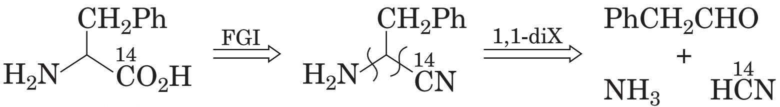
(g)

$(CH_3)_2\overset{\overset{\displaystyle CH_3NH}{|}}{C}-CH_2COCH_3$
TM (23)

(h)

TM (24)

(i)

TM (25)

Solution

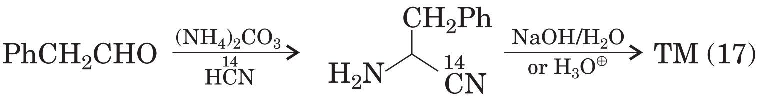
(a) *Retrosynthetic analysis*



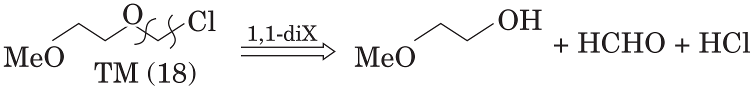
TM (17)

With cyanide as one 'heteroatom' and nitrogen as the other, the disconnection gives an aldehyde, ammonia and hydrogen cyanide.

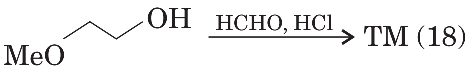
Synthesis



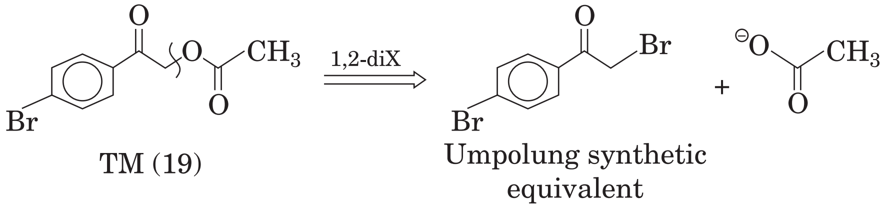
(b) *Retrosynthetic analysis*



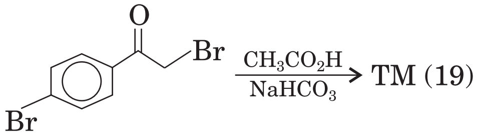
Synthesis



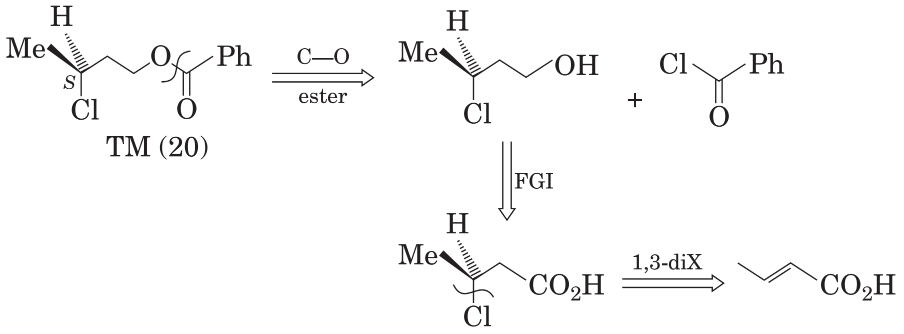
(c) *Retrosynthetic analysis*



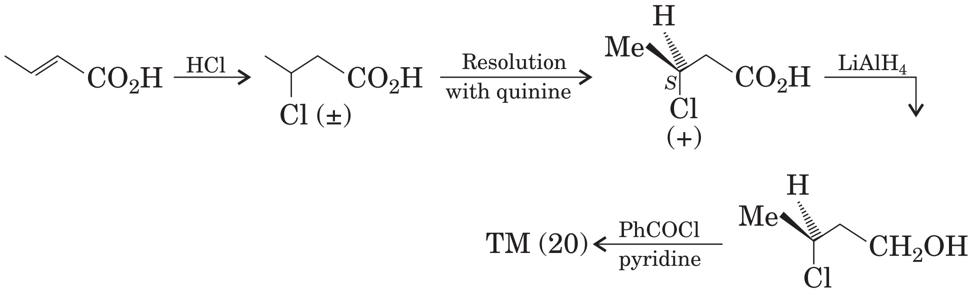
Synthesis



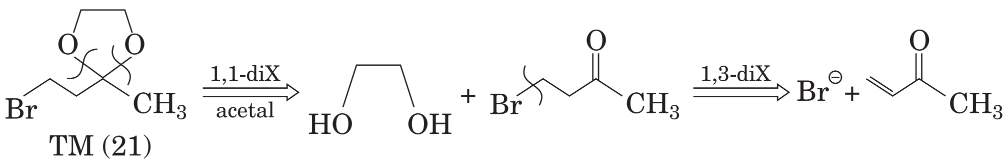
(d) *Retrosynthetic analysis*



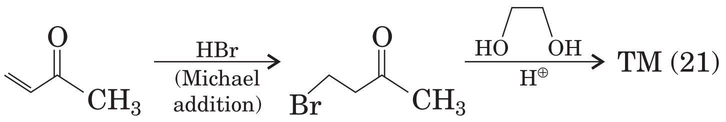
Synthesis



(e) *Retrosynthetic analysis*

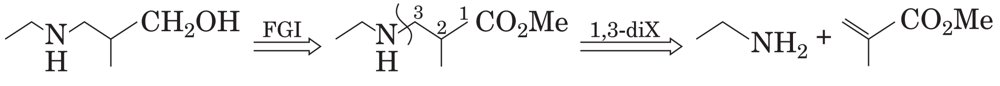


Synthesis



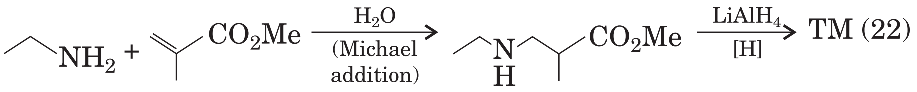
In this synthesis, we shall need acid catalysis as $Br^{\ominus}$ is a very weak nucleophile.

(f) *Retrosynthetic analysis*

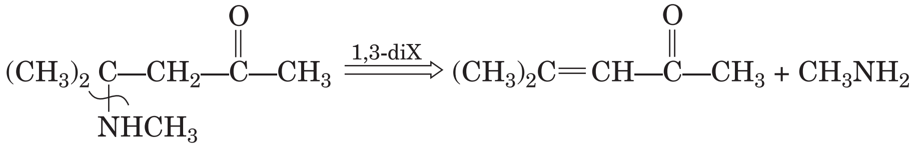


TM (22)

Synthesis



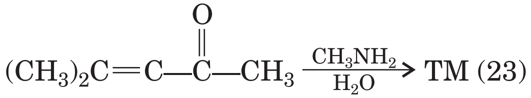
(g) *Retrosynthetic analysis*



$$(CH_3)_2\underset{\displaystyle NHCH_3}{C}-CH_2-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3 \xRightarrow{\text{1,3-diX}} (CH_3)_2C=CH-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3 + CH_3NH_2$$

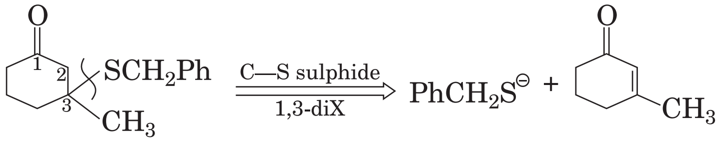
TM (23)

Synthesis



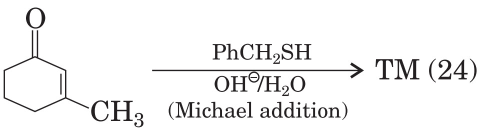
$$(CH_3)_2C=C-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3 \xrightarrow[H_2O]{CH_3NH_2} \text{TM (23)}$$

(h) *Retrosynthetic analysis*

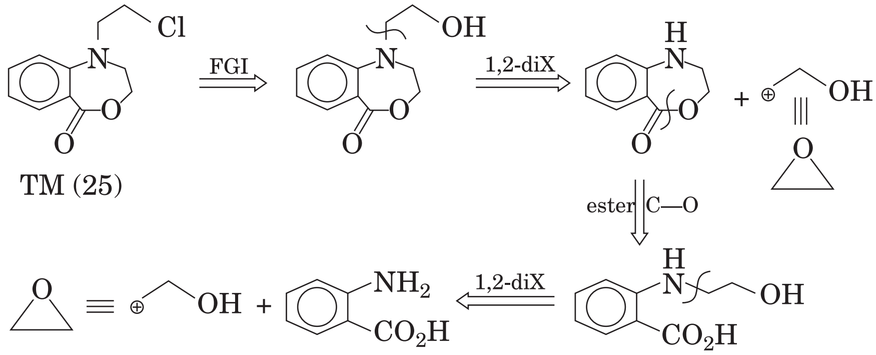


TM (24)

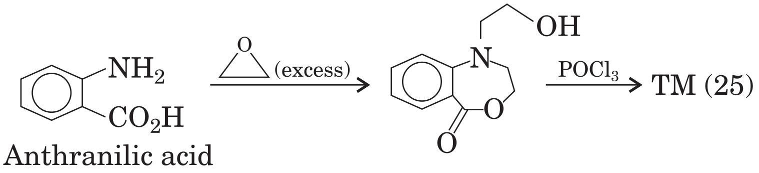
Synthesis



(i) *Retrosynthetic analysis*

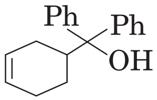


Synthesis



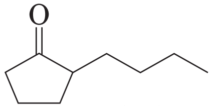
6. Using disconnection approach, design a suitable synthesis for each of the following target molecules:

(a)



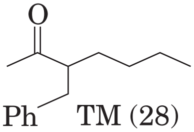
TM (26)

(b)



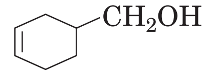
TM (27)

(c)



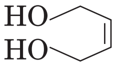
TM (28)

(d)



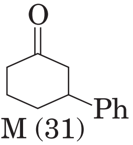
TM (29)

(e)



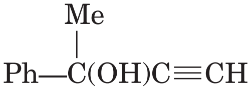
TM (30)

(f)



TM (31)

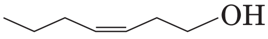
(g)



$\mathrm{Ph{-}\overset{Me}{\overset{|}{C}}(OH)C{\equiv}CH}$

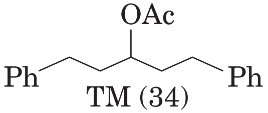
TM (32)

(h)



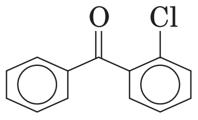
TM (33)

(i)



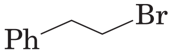
TM (34)

(j)



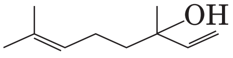
TM (35)

(k)



TM (36)

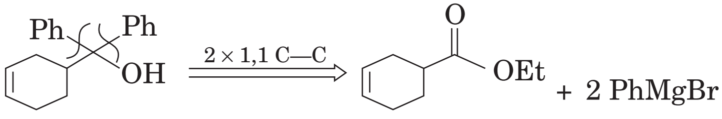
(l)



TM (37)

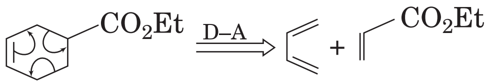
Solution

(a) *Retrosynthetic analysis*

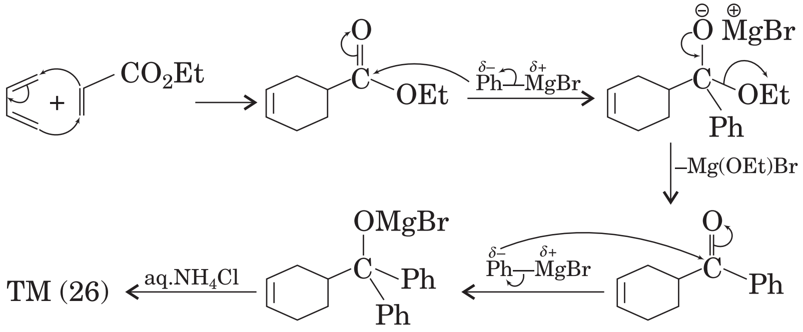


TM (26)

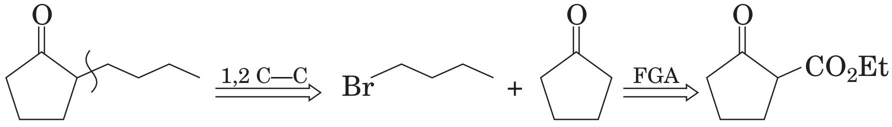
The ester contains a double bond in a six-membered ring and the Diels–Alder disconnection can be used to get the synthetic equivalents directly



Synthesis



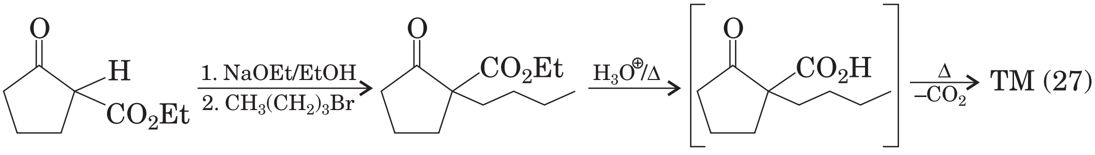
(b) *Retrosynthetic analysis*



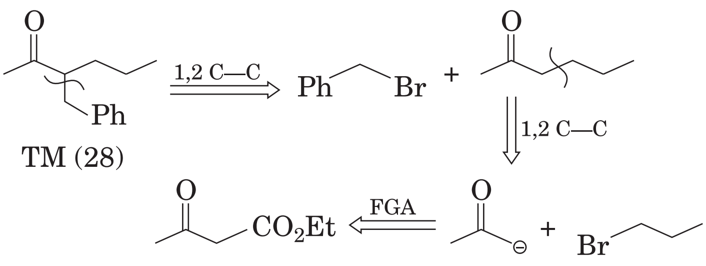
TM (27)

Synthesis

The synthesis is carried out by alkylating at the carbon atom between the two carbonyl groups followed by hydrolysis and decarboxylation.

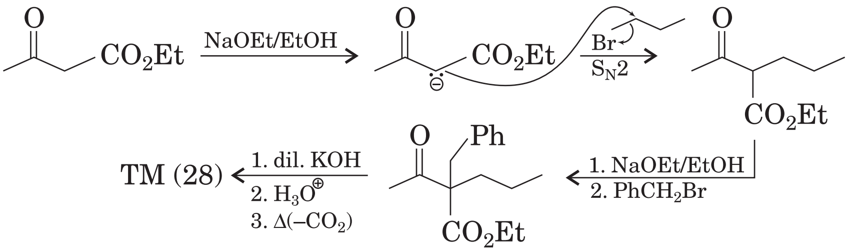


(c) *Retrosynthetic analysis*

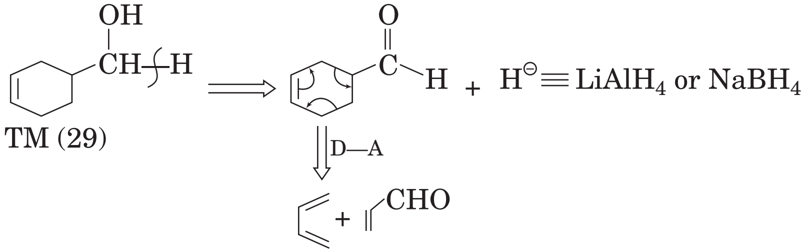


TM (28)

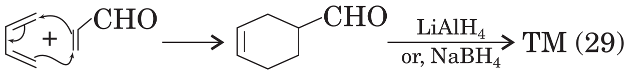
Synthesis



(d) *Retrosynthetic analysis*

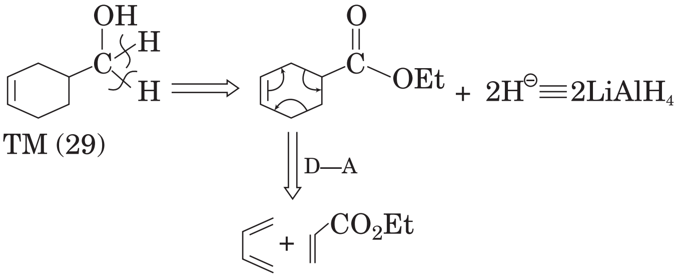


Synthesis

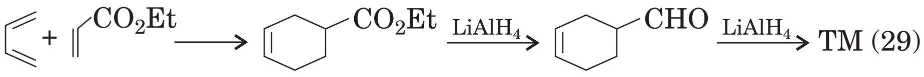


Alternative approach

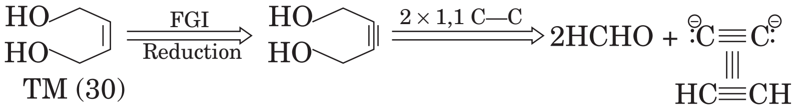
Retrosynthetic analysis



Synthesis



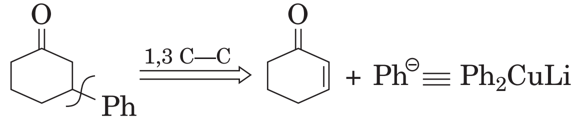
(e) *Retrosynthetic analysis*



Synthesis

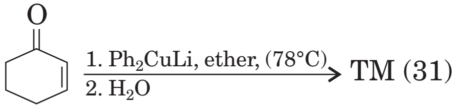
$$\begin{tikzcd}
 & HC\equiv CH \arrow[r, "NaNH_2\ (1\ mole)", "liq.\ NH_3"'] & HC\equiv CNa \arrow[r, "HCHO"] & HC\equiv C-CH_2OH \arrow[d, "NaNH_2\ (1\ mole)", "liq.\ NH_3"'] \\
TM\ (30) & HOCH_2-C\equiv C-CH_2OH \arrow[l, "H_2"', "Lindlar\ cat."] & & NaC\equiv C-CH_2OH \arrow[ll, "HCHO"']
\end{tikzcd}$$

(f) *Retrosynthetic analysis*

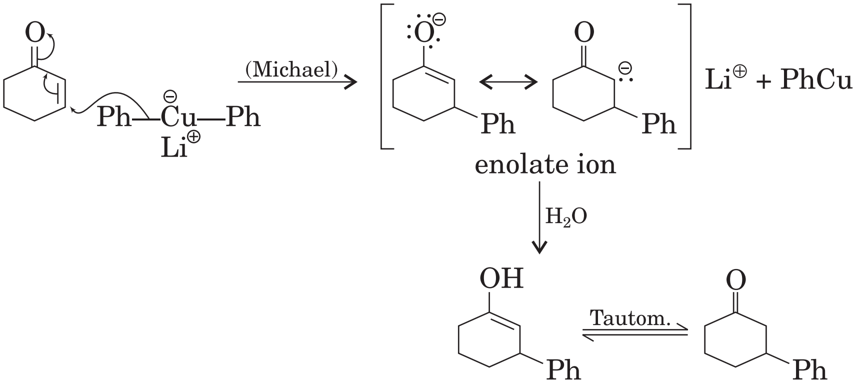


TM (31)

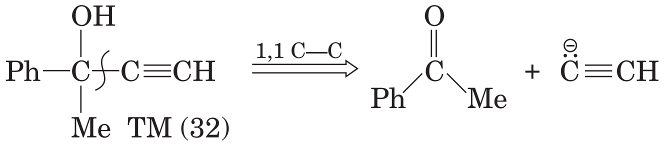
Synthesis



Mechanism of the reaction



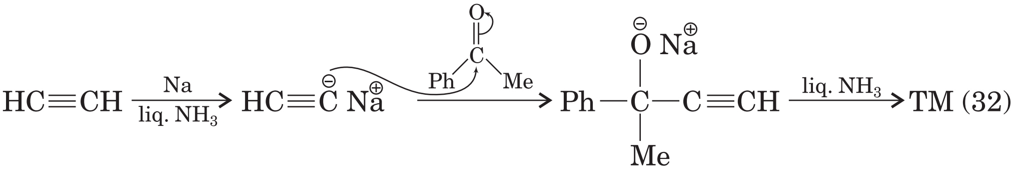
(g) *Retrosynthetic analysis*



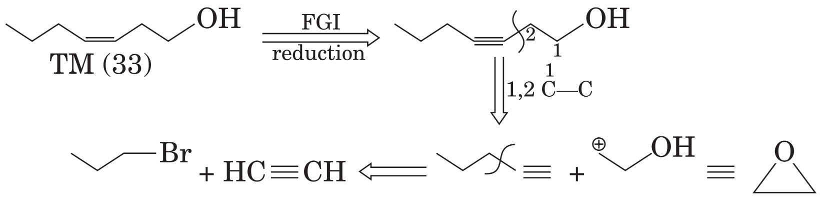
TM (32)

The disconnection is done in this fashion because the acetylide ion $(HC\equiv\overset{\ominus}{\ddot{C}}:)$ is the most stable one (since the negative carbon is *sp*-hybridized and most electronegative).

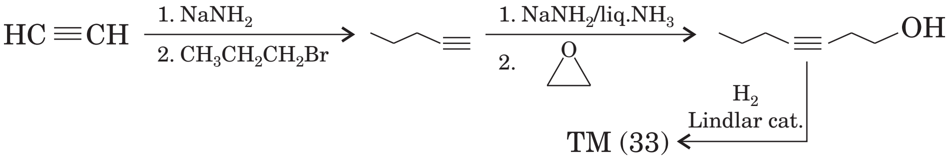
Synthesis



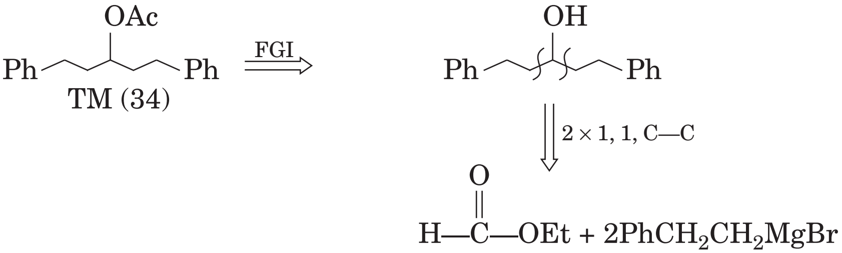
(h) *Retrosynthetic analysis*



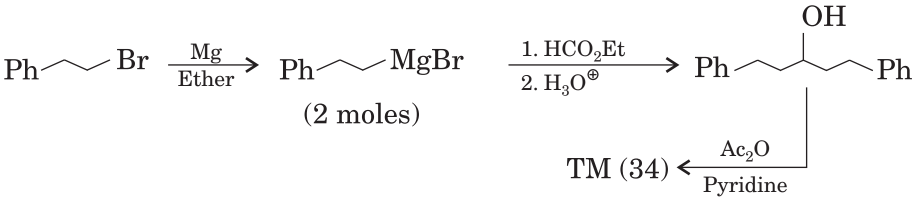
Synthesis



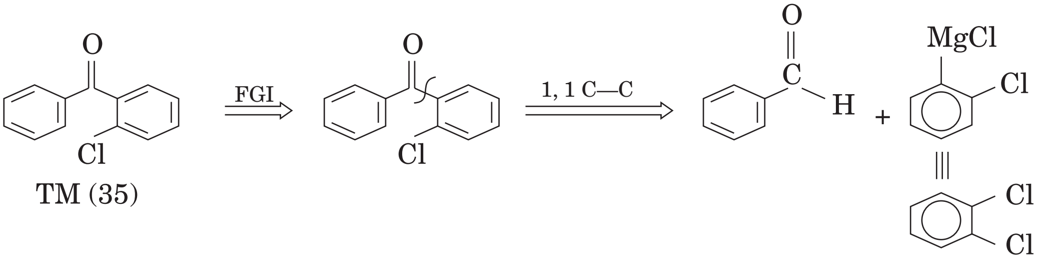
(i) *Retrosynthetic analysis*



Synthesis

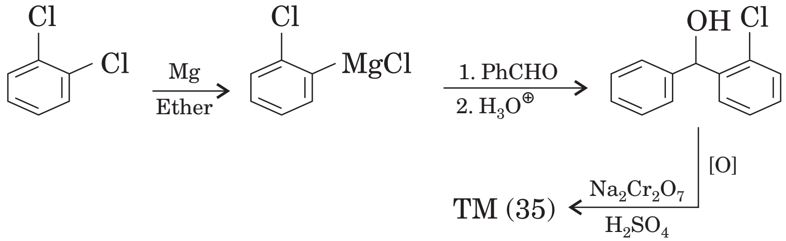


(j) *Retrosynthetic analysis*

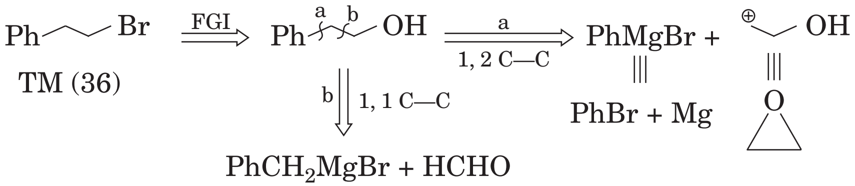


Since 1,1 C—C disconnection of a ketone is often not much reliable, disconnection is done after converting it to the alcohol oxidation level.

Synthesis

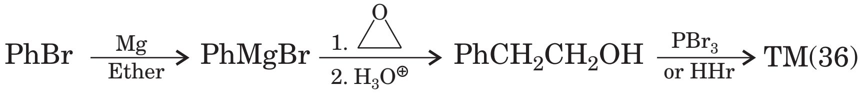


(k) *Retrosynthetic analysis*

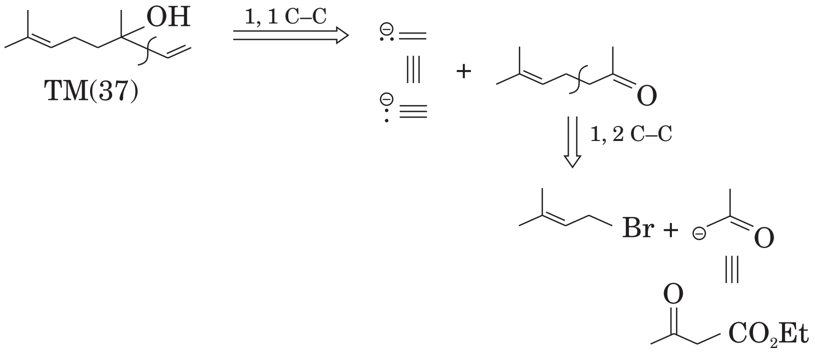


The disconnection (a) is better than the disconnection (b) and this is because benzyl Grignard reagents easily give diradicals which then polymerise.

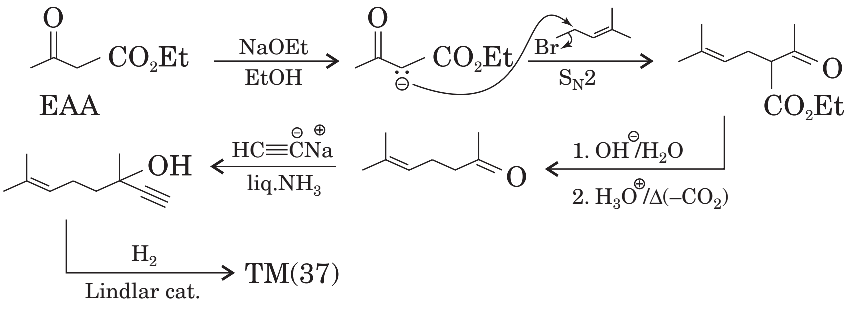
Synthesis



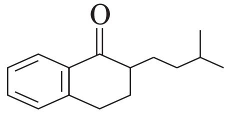
(l) *Retrosynthetic analysis*

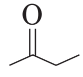


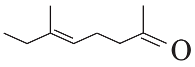
Synthesis

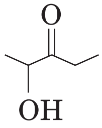


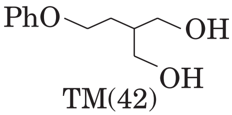
7. Outline the retrosynthetic analysis and the designed synthesis of the following target molecules:

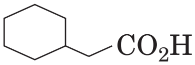
(a)

TM(38)

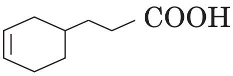
(b)

TM(39)

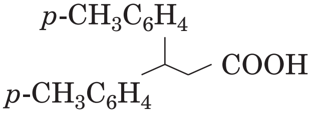
(c)

TM(40)

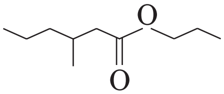
(d)

TM(41)

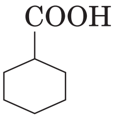
(e)

TM(42)

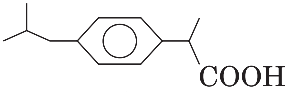
(f)

TM(43)

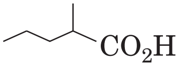
(g)

TM(44)

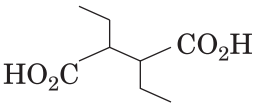
(h)

TM(45)

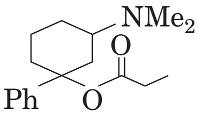
(i)

TM(46)

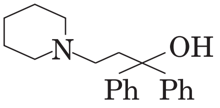
(j)

TM(47)

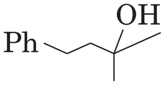
(k)

TM(48)

(l)

TM(49)

(m)

TM(50)

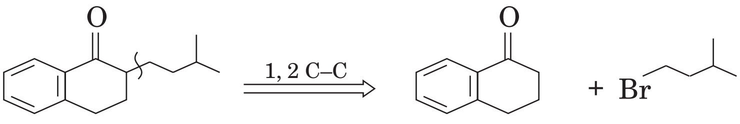
(n)

TM(51)

(o)

TM(52)

(p)

TM(53)

Solution

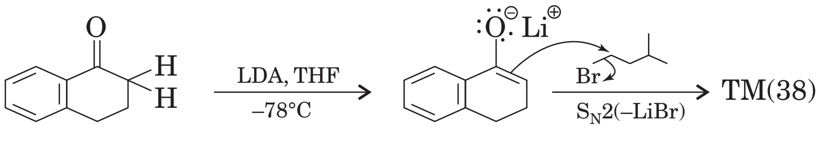
(a) *Retrosynthetic analysis*



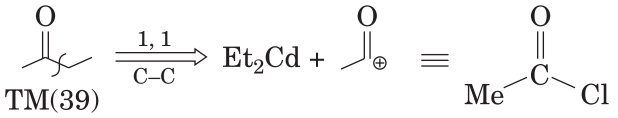
TM(38)

(can form enolate on one side only)

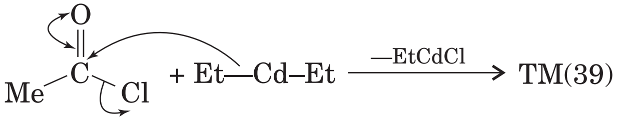
Synthesis



(b) *Retrosynthetic analysis*



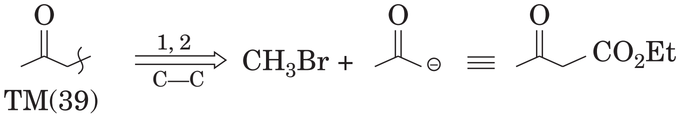
Synthesis



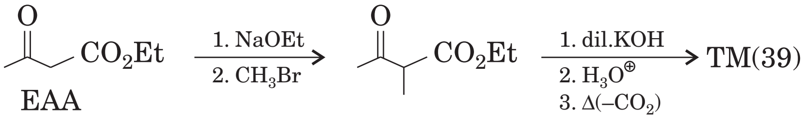
The ester $MeCO_2Et$ and the Grignard reagent MeMgI are not used for this synthesis because the intermediate ketone (more reactive than the ester) may react with MeMgI to give an alcohol.

Alternative approach

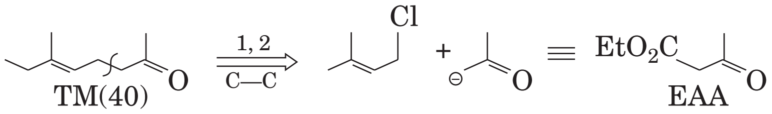
Retrosynthetic analysis



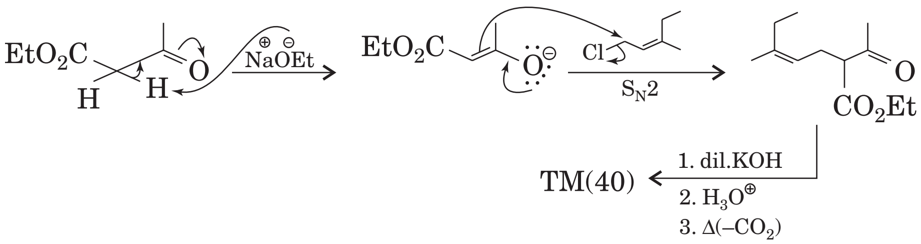
Synthesis



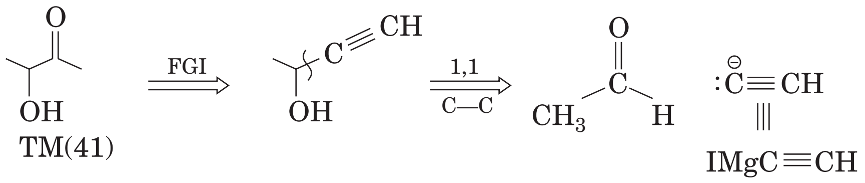
(c) *Retrosynthetic analysis*



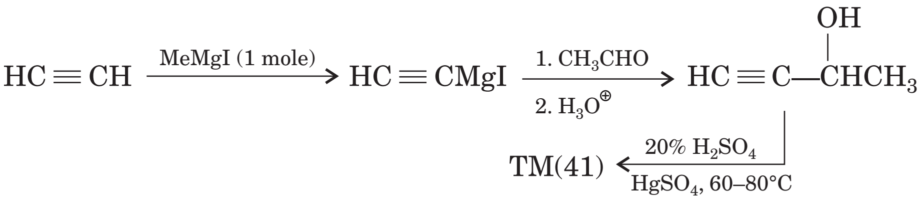
Synthesis



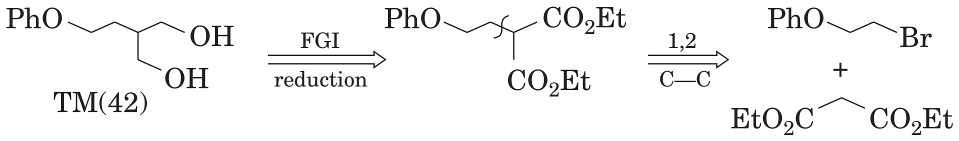
(d) *Retrosynthetic analysis*



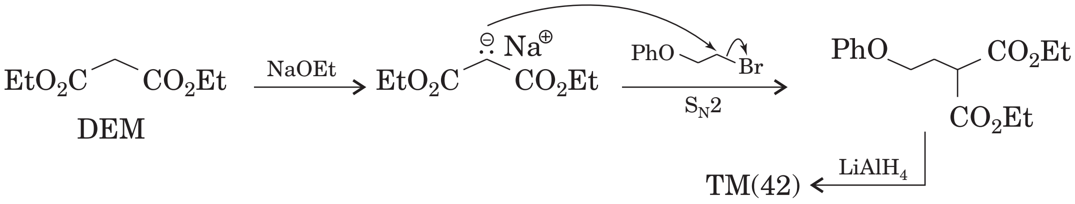
Synthesis



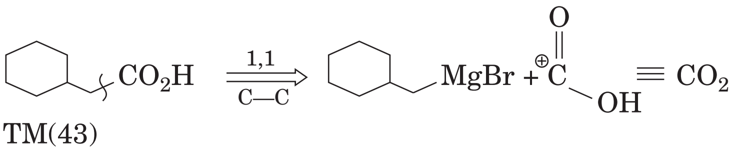
(e) *Retrosynthetic analysis*



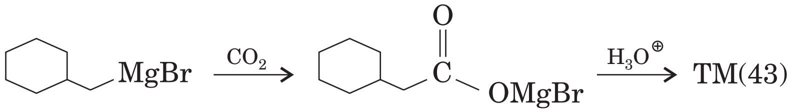
Synthesis



(f) *Retrosynthetic analysis*

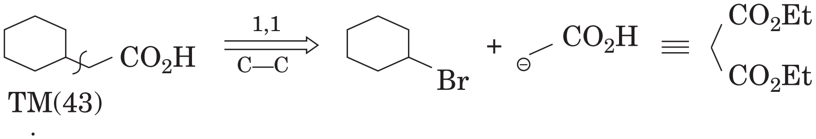


Synthesis

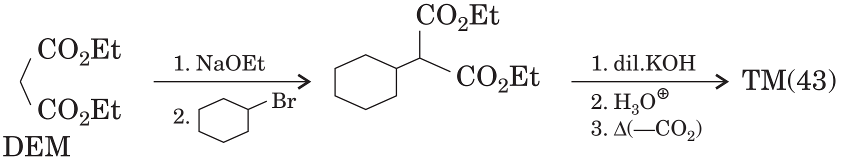


Alternative approach

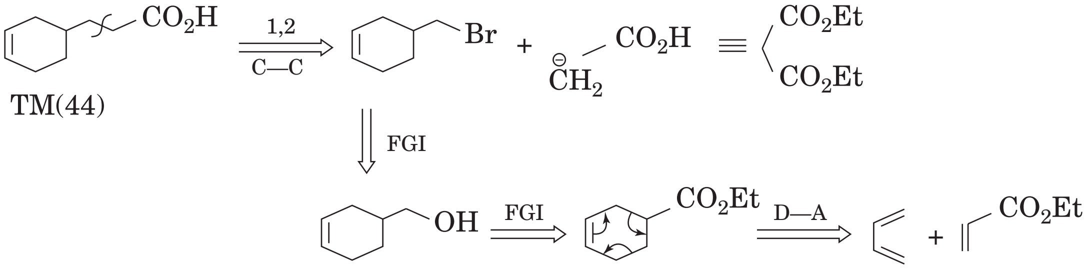
Retrosynthetic analysis



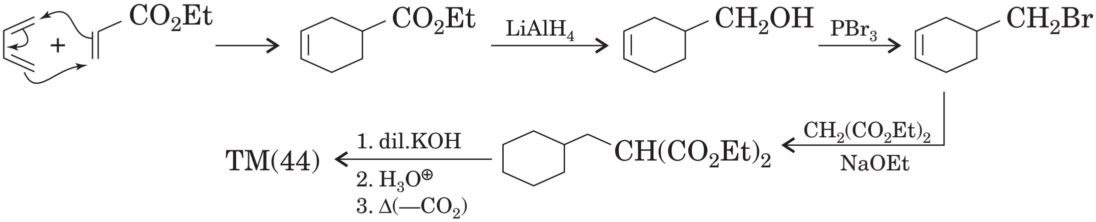
Synthesis



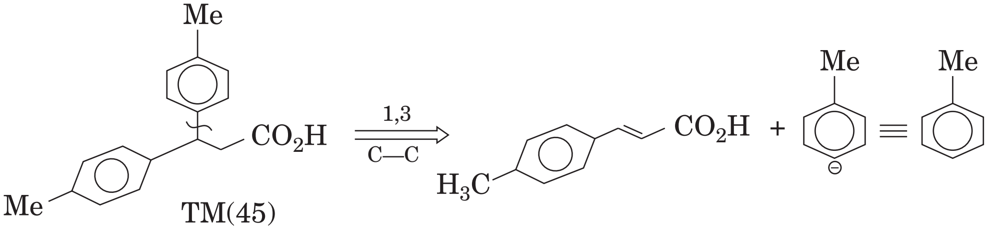
(g) *Retrosynthetic analysis*



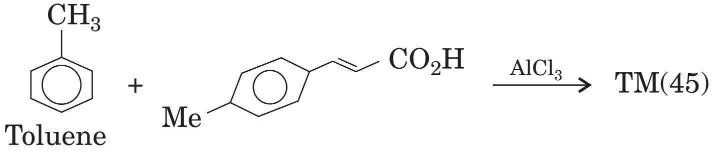
Synthesis



(h) *Retrosynthetic analysis*

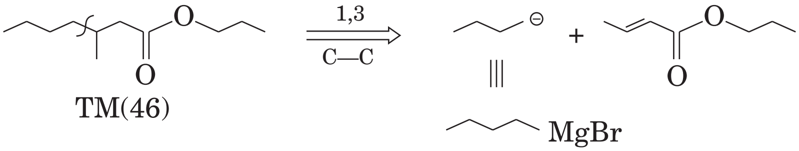


Synthesis



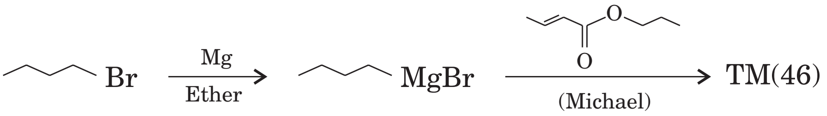
Aromatic hydrocarbons are good nucleophiles to add in this fashion under Friedel–Crafts conditions. Therefore, an organometallic reagent is not necessary to use in this synthesis.

(i) *Retrosynthetic analysis*

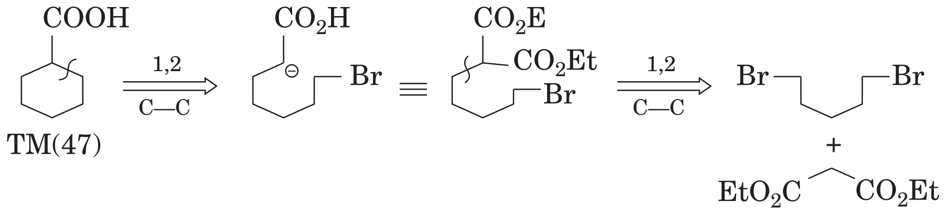


It is better to disconnect the longer chain to get back to simple starting materials.

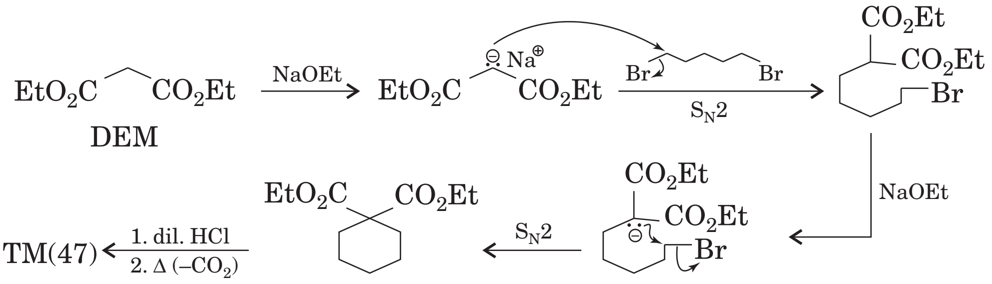
Synthesis



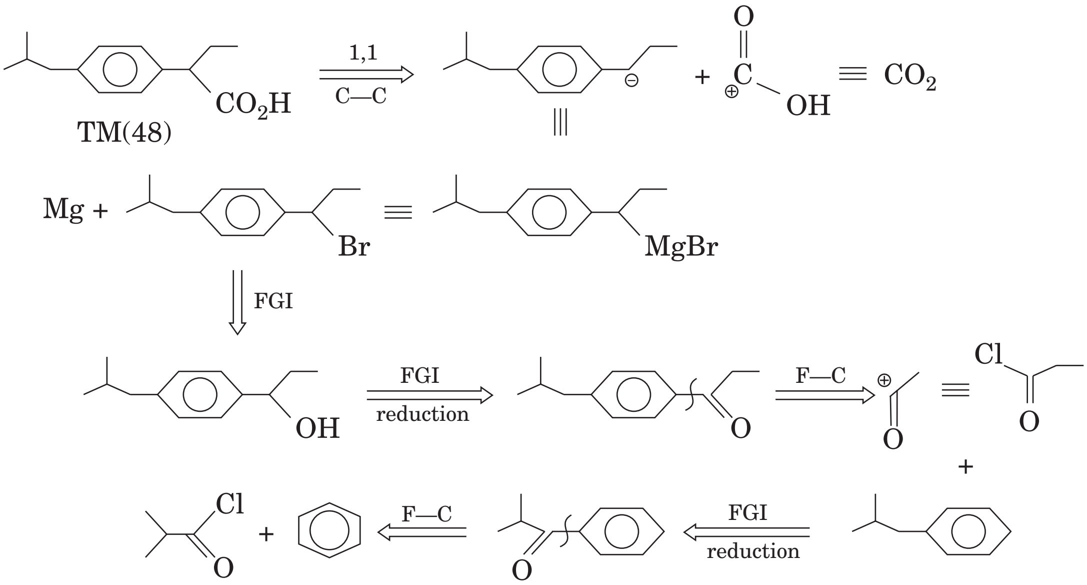
(j) *Retrosynthetic analysis*



Synthesis

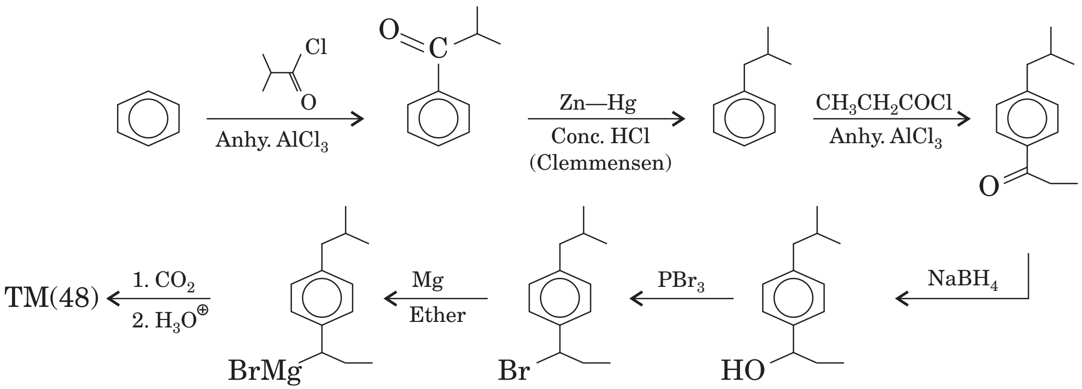


(k) *Retrosynthetic analysis*

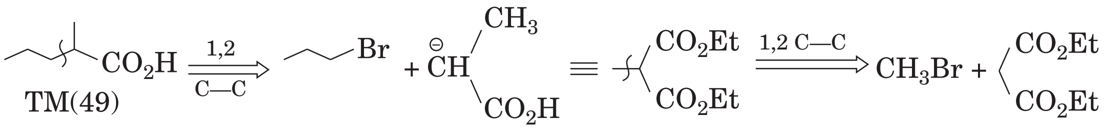


The isobutyl group is introduced by acylation followed by Clemmensen reduction and this is because its introduction leads to a rearranged product.

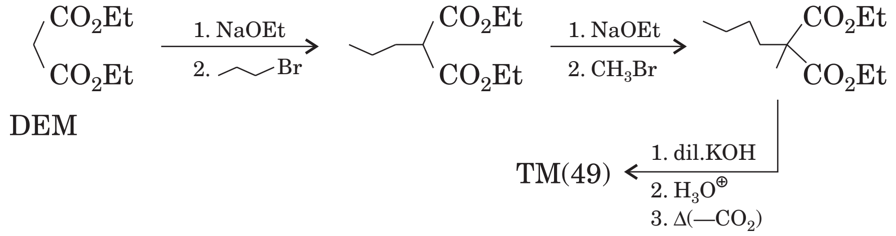
Synthesis



(l) *Retrosynthetic analysis*

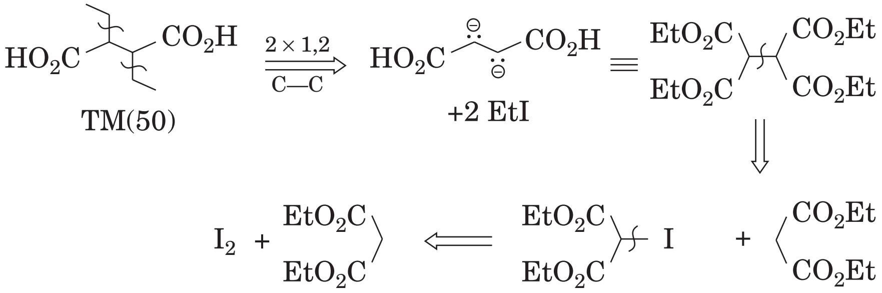


Synthesis

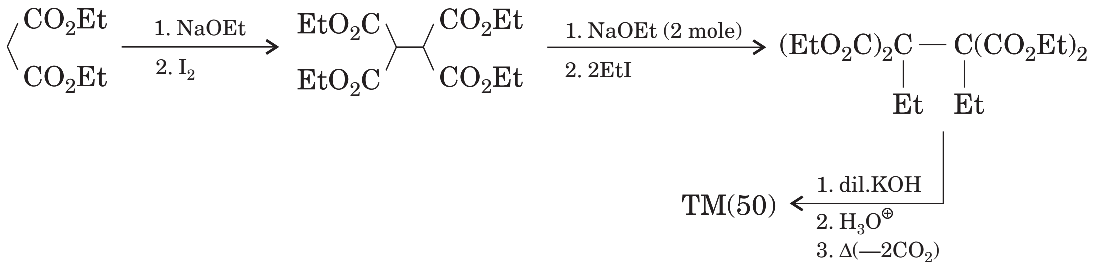


Because of steric reason, it is better to introduce the larger group before the smaller.

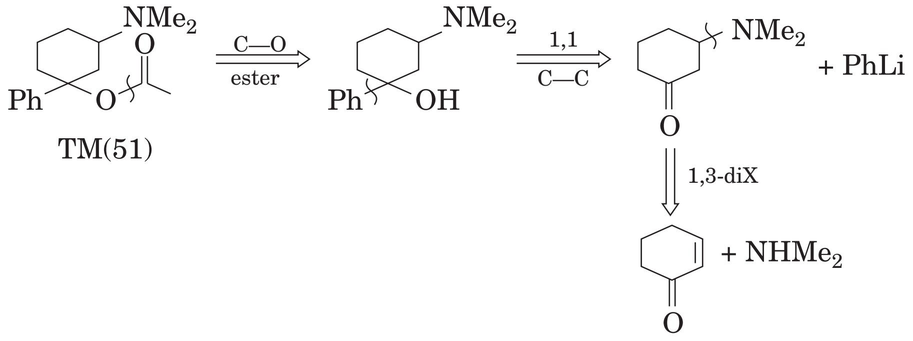
(m) *Retrosynthetic analysis*



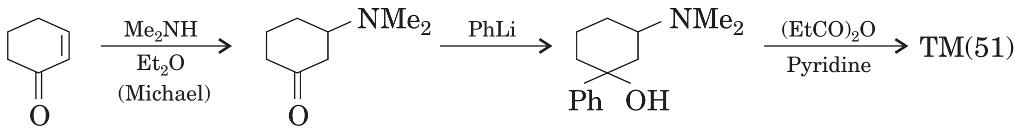
Synthesis



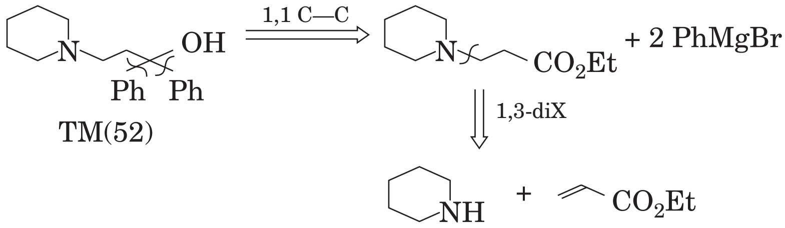
(n) *Retrosynthetic analysis*



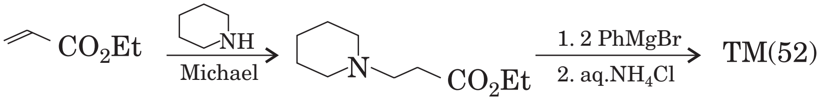
Synthesis



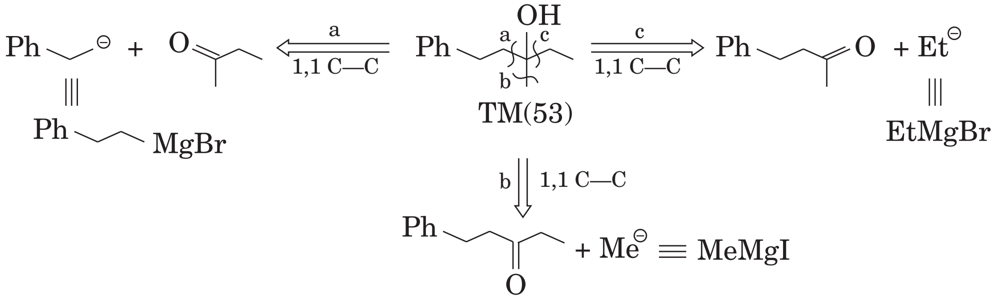
(o) *Retrosynthetic analysis*



Synthesis

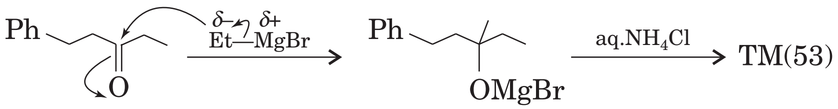


(p) *Retrosynthetic analysis*

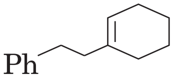


The disconnection (c) leads back to a ketone, which is cheaply made starting material from acetone and benzaldehyde, and this is the route which is actually chosen for synthesis.

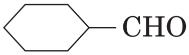
Synthesis



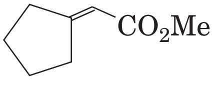
8. Using disconnection approach, design a suitable synthesis for each of the following compounds.

(a) 

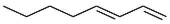
TM(54)

(b) 

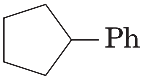
TM(55)

(c) 

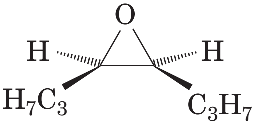
TM(56)

(d) 

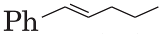
TM(57)

(e) 

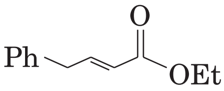
TM(58)

(f) 

TM(59)

(g) 

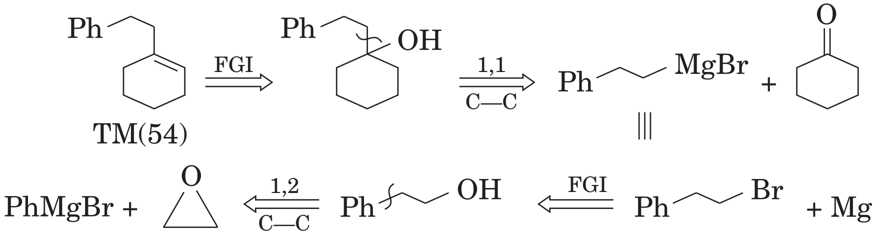
TM(60)

(h) 

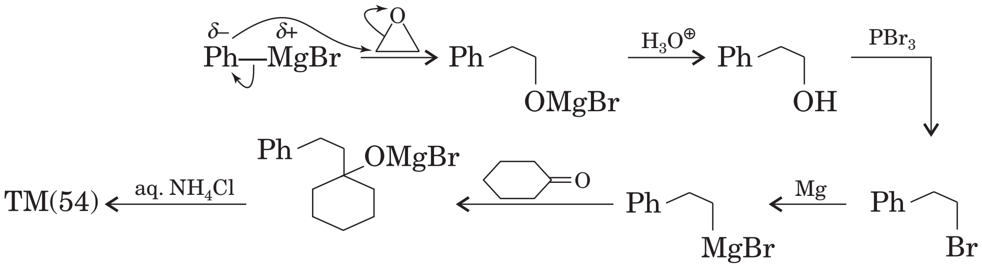
TM(61)

Solution

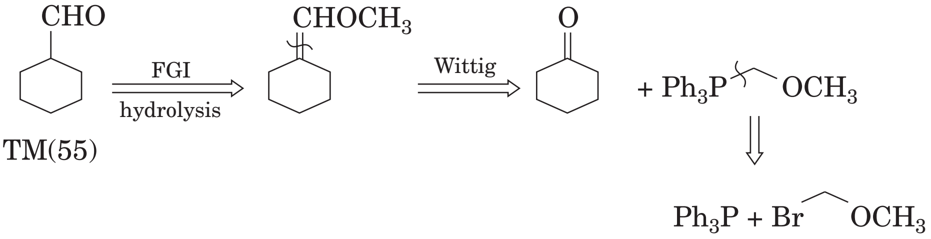
(a) *Retrosynthetic analysis*



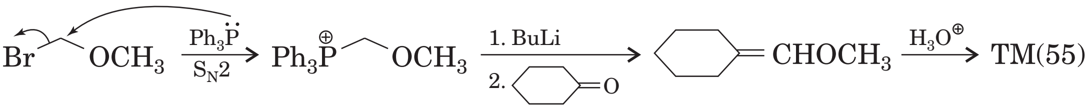
Synthesis



(b) *Retrosynthesis analysis*

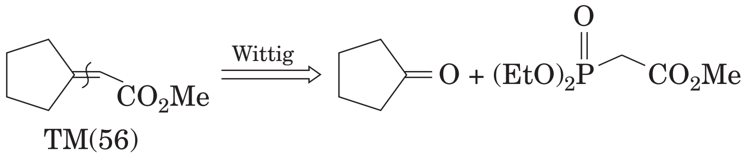


Synthesis

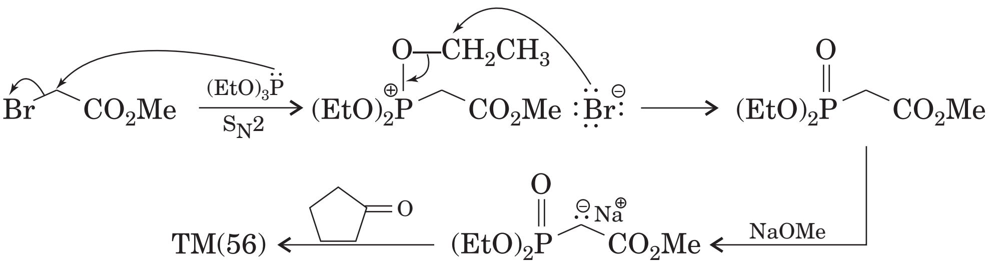


(c) Wittig reaction can be used to prepare this α,β-unsaturated ester. A phosphonate ester with a stabilising group is used in this reaction.

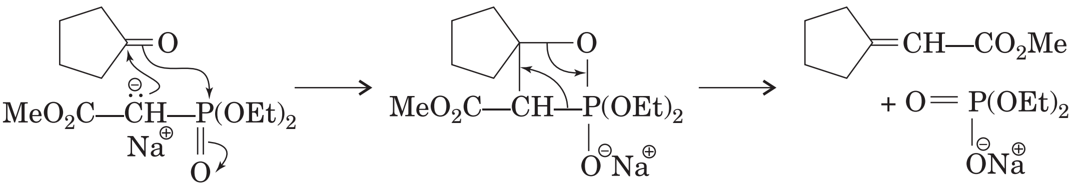
Retrosynthetic analysis



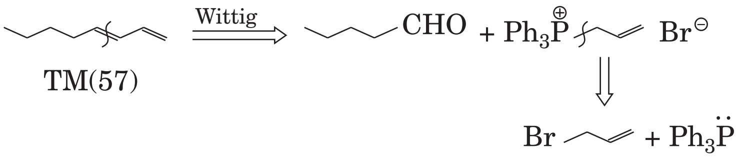
Synthesis



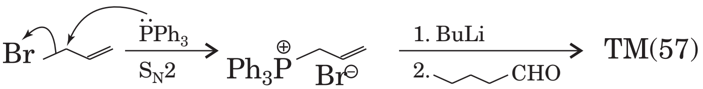
Mechanism of the Wittig reaction



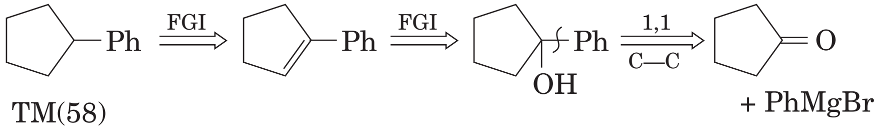
(d) Since the central double bond is *trans*, the direction of disconnection is to be chosen to give a stabilised ylide. Therefore, the central double bond is to be disconnected.
Retrosynthetic analysis



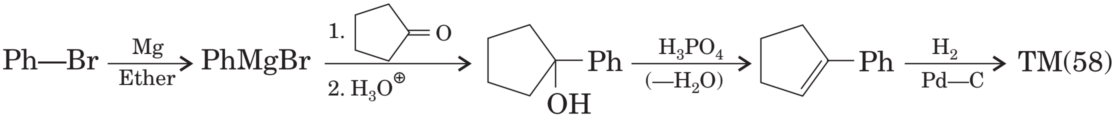
Synthesis



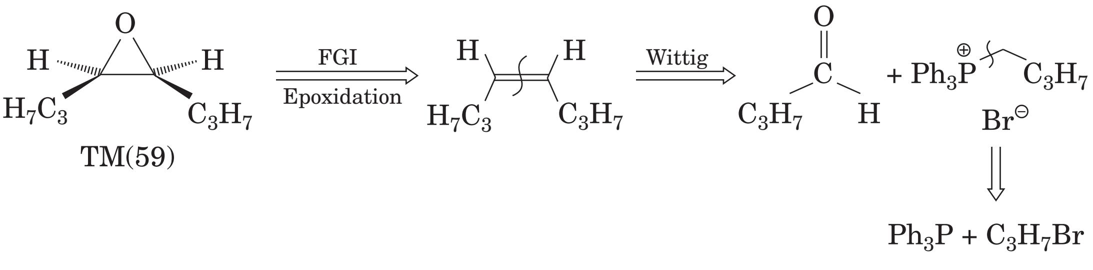
(e) *Retrosynthetic analysis*



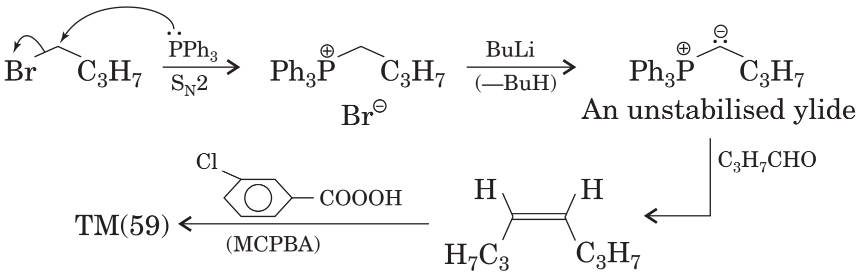
Synthesis



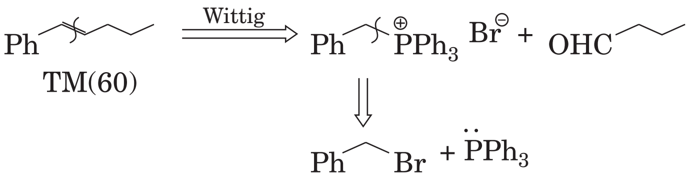
(f) This epoxide can be prepared by stereospecific epoxidation of a *cis* alkene which on disconnection in either sense gives an unstabilised ylide and therefore, selectivity is expected in the Wittig reaction.
Retrosynthetic analysis



Synthesis

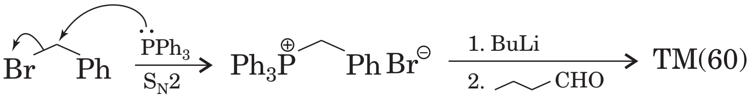


(g) *Retrosynthetic analysis*

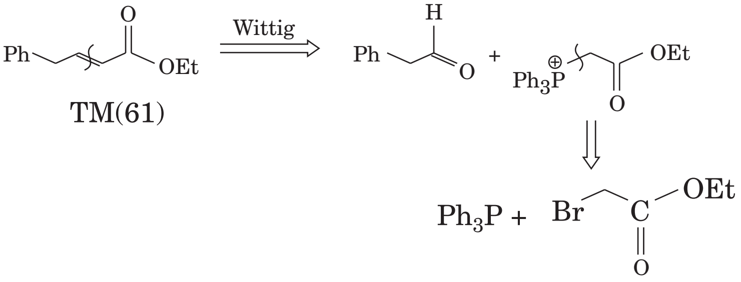


This stabilised ylide gives mainly the *E* isomer.

Synthesis

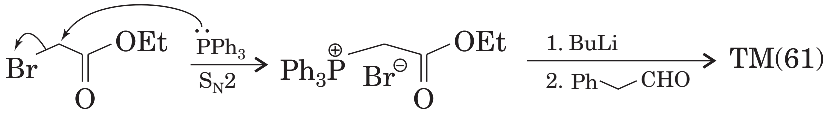


(h) *Retrosynthetic analysis*

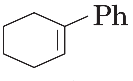


This stabilised ylide gives mainly the *E* (*trans*) alkene.

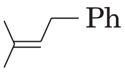
Synthesis



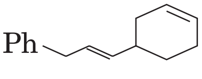
9. Give retrosynthetic analysis and an efficient synthesis for each of the following compounds. Which of the possible two disconnections is expected to be a good choice and why?

(a) 

TM(62)

(b) 

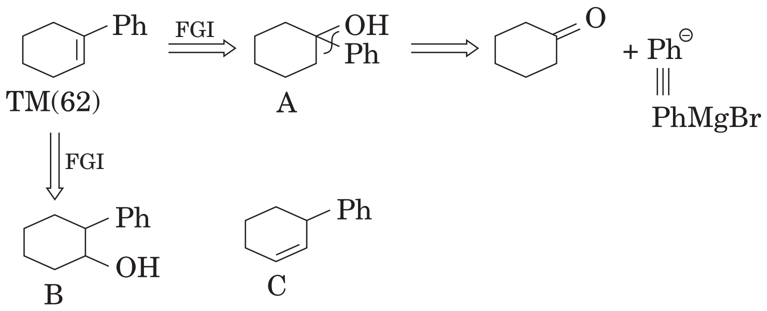
TM(63)

(c) 

TM(64)

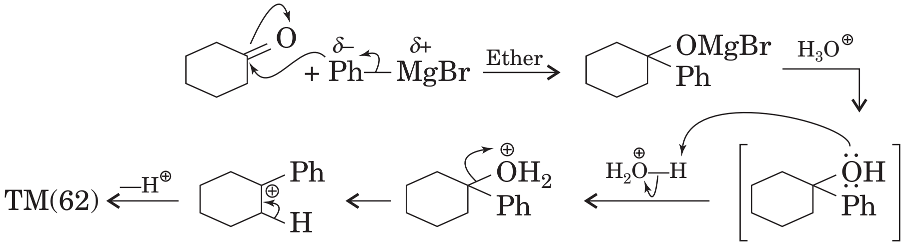
Solution

(a) *Retrosynthetic analysis*

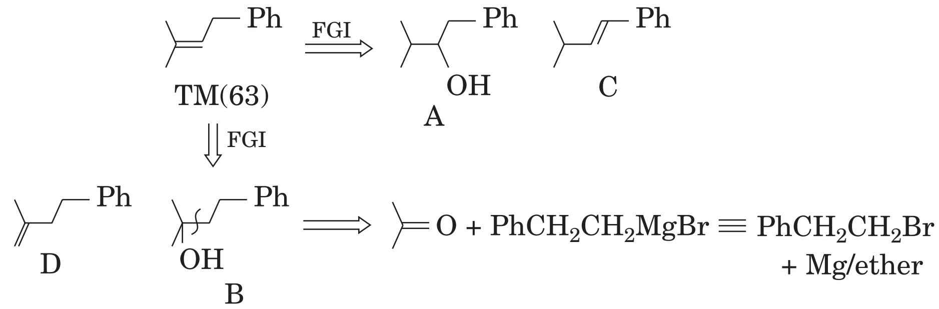


There are two possible disconnections. However, the disconnection involving A is more appropriate and helpful because dehydration of A can give only the target molecule but dehydration of B might give the compound C along with the target molecule.

Synthesis

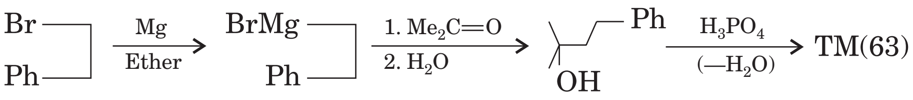


(b) *Retrosynthetic analysis*



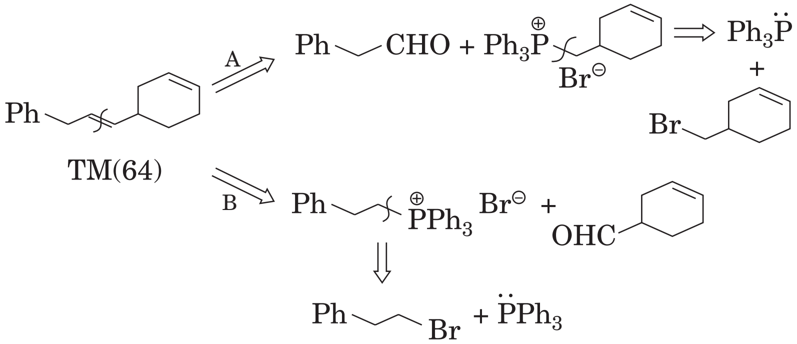
Dehydration of A could also give C, the conjugated olefin, but dehydration of B will give only the target molecule and none of the less substituted olefin D.

Synthesis



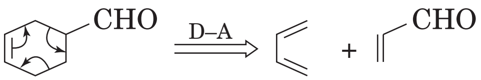
(c) *Retrosynthetic analysis*

The double bond outside the ring is to be disconnected as this will give two fragments. The two possible routes for such disconnection are as follows:

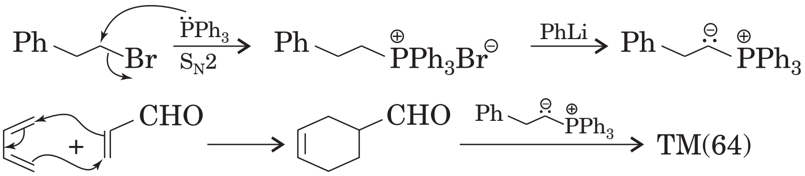


TM(64)

The route B is better than route A because the starting materials are readily available. The aldehyde, for example, can easily be prepared by a Diels–Alder reaction.



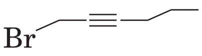
Synthesis


Ph
Br
$\ddot{P}Ph_3$
S_N2
Ph
$\overset{\oplus}{P}Ph_3Br^{\ominus}$
PhLi
Ph
$\overset{\oplus}{P}Ph_3$
CHO
+
CHO
Ph
$\overset{\oplus}{P}Ph_3$

TM(64)

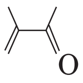
10. Using disconnection approach, design a suitable synthesis for each of the following target molecules:

(a)



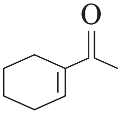
TM(65)

(b)



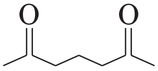
TM(66)

(c)



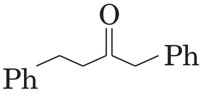
TM(67)

(d)



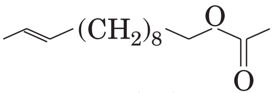
TM(68)

(e)



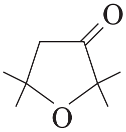
TM(69)

(f)



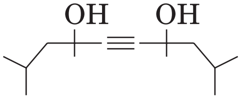
TM(70)

(g)



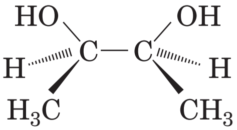
TM(71)

(h)



TM(72)

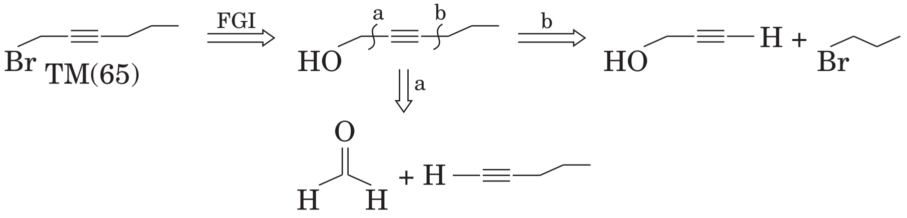
(i)



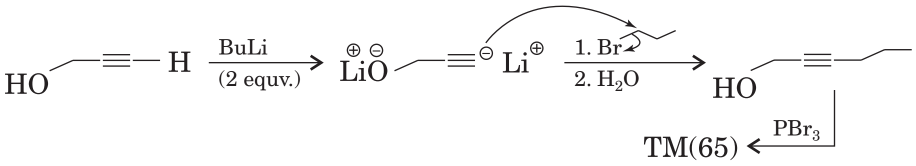
TM(73)

Solution

(a) *Retrosynthetic analysis*

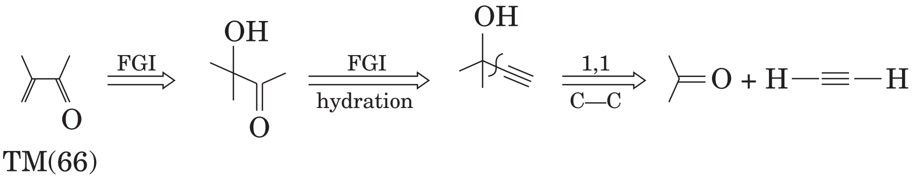


Synthesis

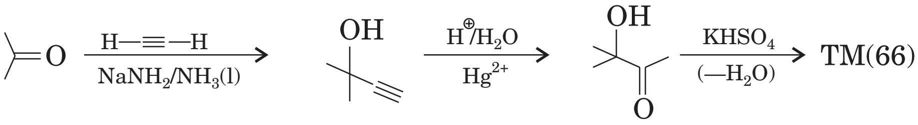


Either disconnection (a) or (b) could be used for the synthesis of (65). The dianion involved in the synthesis corresponding to the disconnection (b) is alkylated at the carbon. This is because the carbanion is much more reactive (p*K*a of acetylene is ~25) than the oxyanion (p*K*a of an alcohol is ~16) and protection of alcohol is not required.

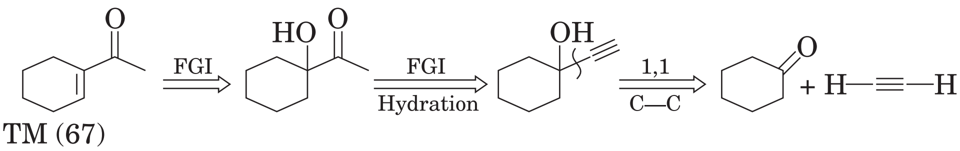
(b) *Retrosynthetic analysis*



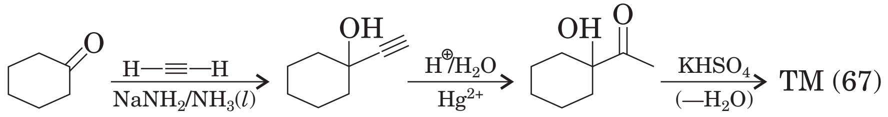
Synthesis



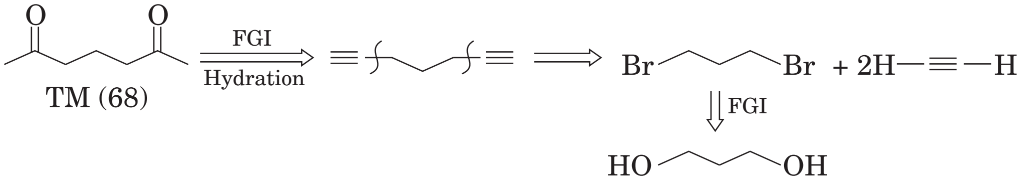
(c) *Retrosynthetic analysis*



Synthesis

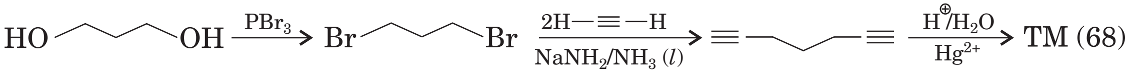


(d) *Retrosynthetic analysis*

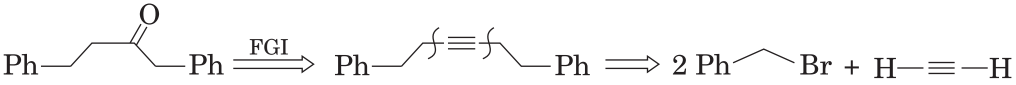


TM (68)

Synthesis

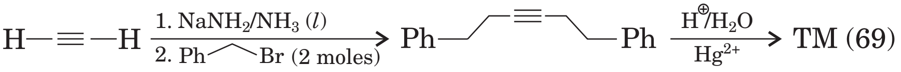


(e) *Retrosynthetic analysis*

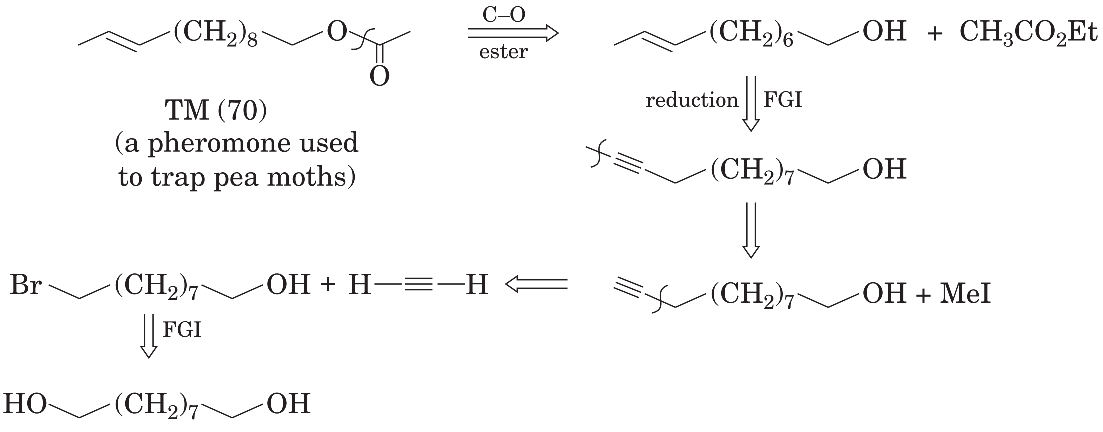


TM (69)

Synthesis



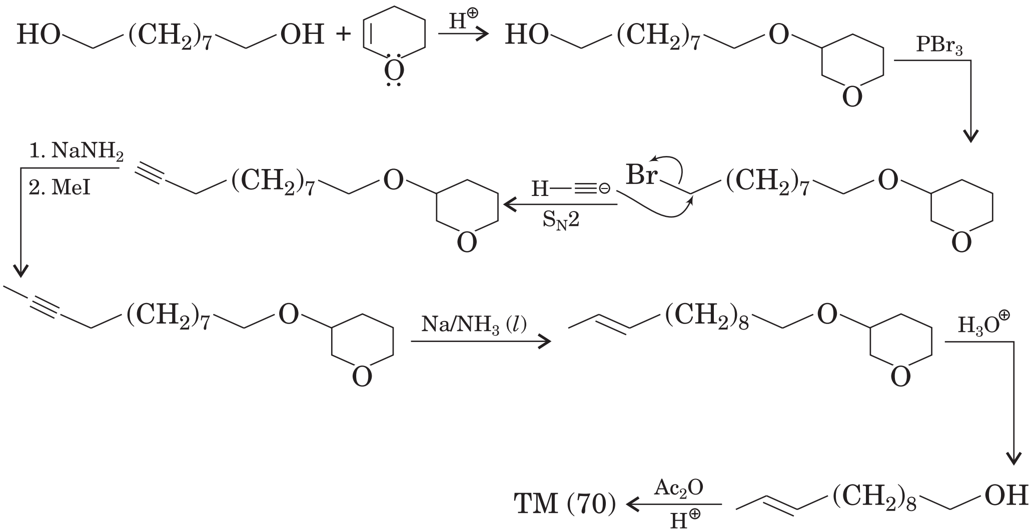
(f) *Retrosynthetic analysis*



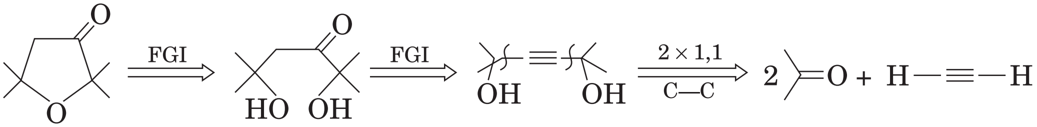
TM (70)
(a pheromone used
to trap pea moths)

Synthesis

The starting material to be used in this synthesis is a diol. Since only one —OH group should react, the other —OH group should be protected. Dihydropyran is to be used for this protection.

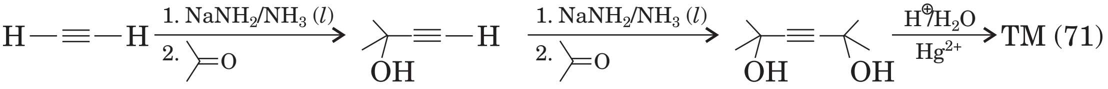


(g) *Retrosynthetic analysis*

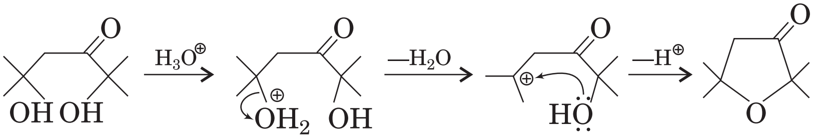


TM (71)

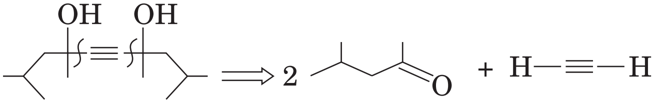
Synthesis



In the hydration step, the ether forms spontaneously as follows:

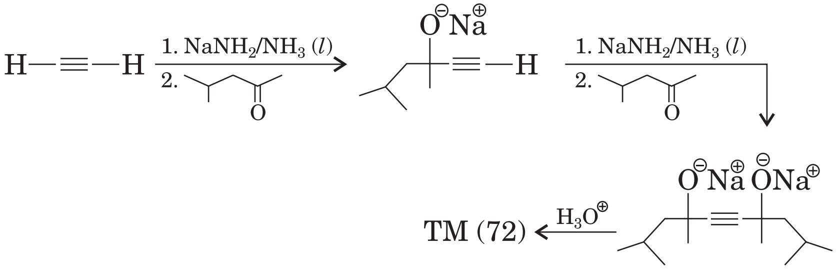


(h) *Retrosynthetic analysis*

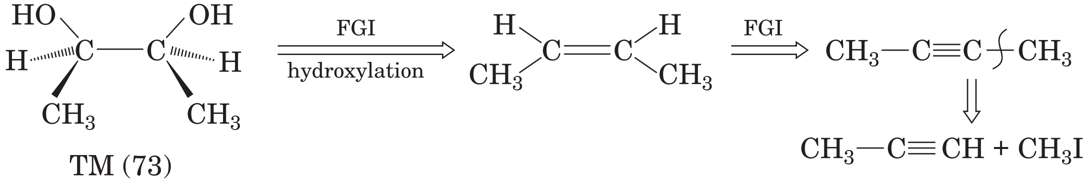


TM (72)
(Surfynol, a defoming
surfactant)

Synthesis

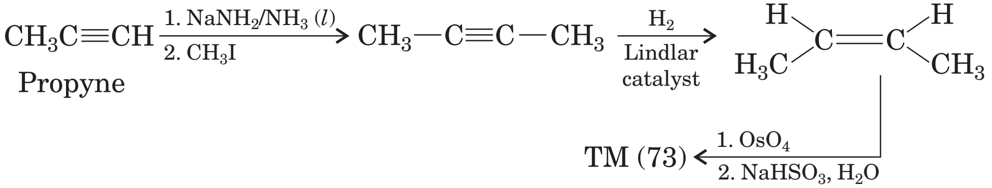

H—≡—H
1. NaNH$_2$/NH$_3$ (*l*)
2.
O
$\overset{\ominus}{O}\overset{\oplus}{Na}$
H
1. NaNH$_2$/NH$_3$ (*l*)
2.
O
$\overset{\ominus}{O}\overset{\oplus}{Na}$ $\overset{\ominus}{O}\overset{\oplus}{Na}$
TM (72)
$H_3O^{\oplus}$

(i) *Retrosynthetic analysis*



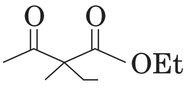
TM (73)

Synthesis



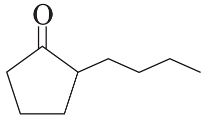
11. Write down the synthesis of each of the following compounds with proper retrosynthetic analysis:

(a)



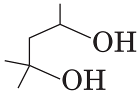
TM (74)

(b)



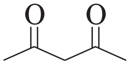
TM (75)

(c)



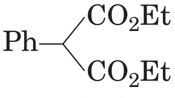
TM (76)

(d)



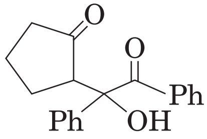
TM (77)

(e)



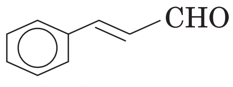
TM (78)

(f)



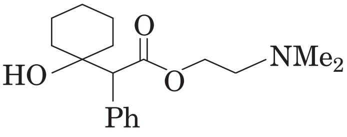
TM (79)

(g)



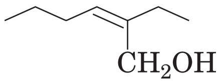
TM (80)

(h)



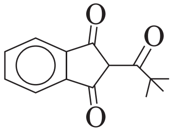
TM (81)

(i)



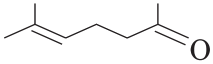
TM (82)

(j)



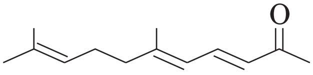
TM (83)

(k)



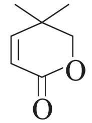
TM (84)

(l)



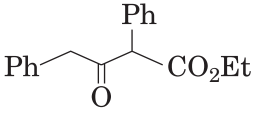
TM (85)

(m)



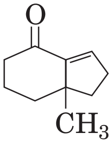
TM (86)

(n)



TM (87)

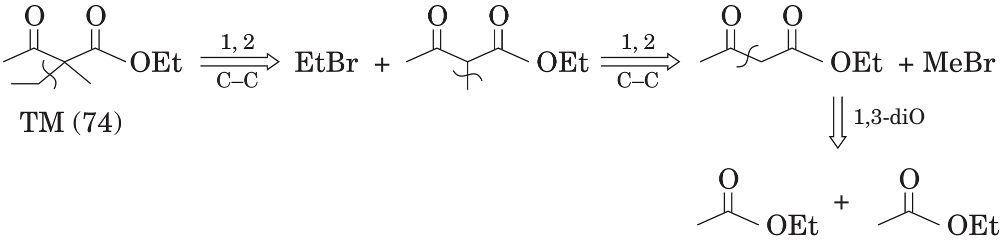
(o)



TM (88)

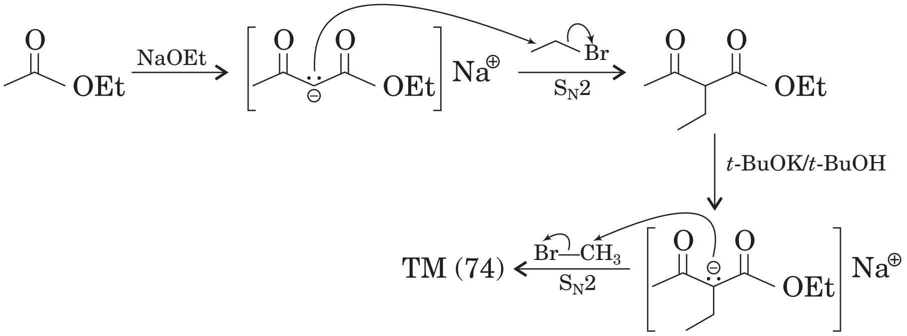
Solution

(a) *Retrosynthetic analysis*

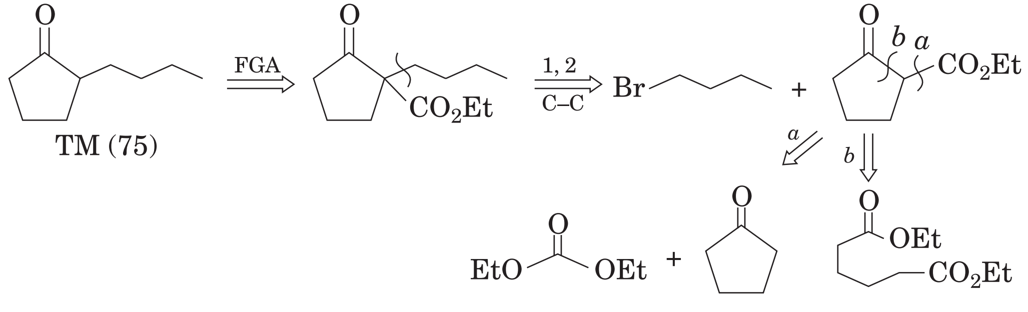


Because of steric reason, the larger alkyl group, $–C_2H_5$, is to be introduced before the smaller alkyl group, $–CH_3$.

Synthesis

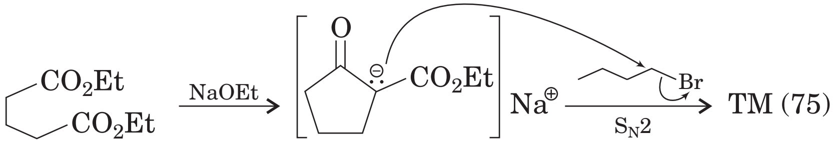


(b) *Retrosynthetic analysis*

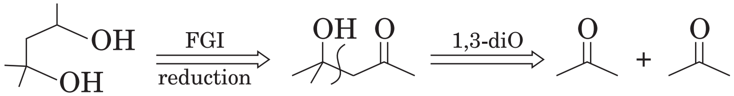


Synthesis

The disconnection (b) of the ketoester gives a symmetrical and readily available diester (diethyl adipate) as starting material. Therefore, it is better than the disconnection (a) Again, this reaction being intramolecular occurs readily.

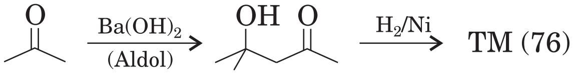


(c) *Retrosynthetic analysis*

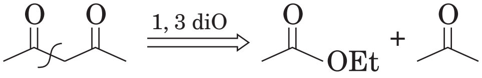


TM (76)

Synthesis

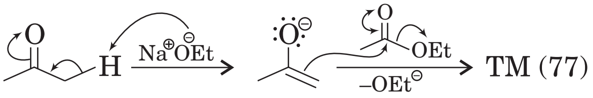


(d) *Retrosynthetic analysis*

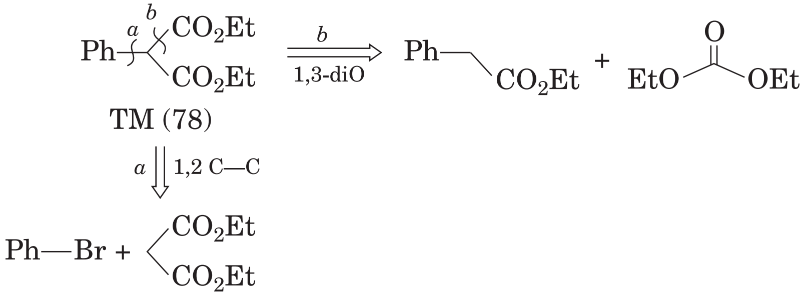


TM (77)

Synthesis



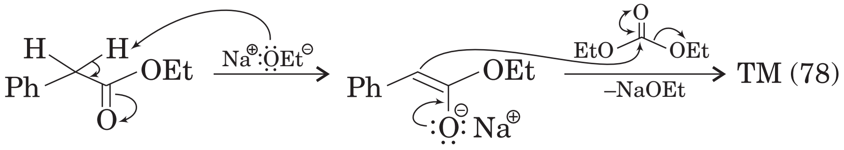
(e) *Retrosynthetic analysis*



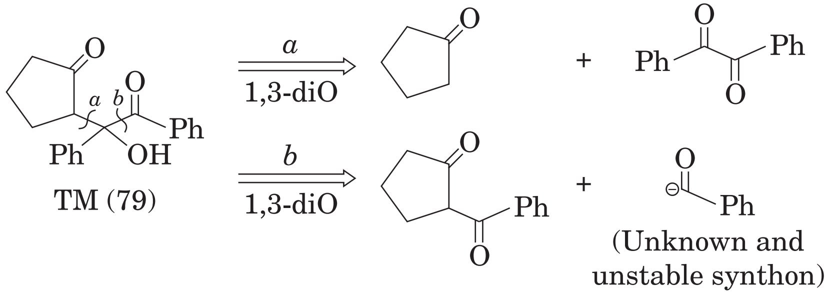
TM (78)

The synthesis corresponding to the disconnection (a) is a nucleophilic substitution on aryl halide involving benzyne intermediate, and therefore, this requires special conditions. On the other hand, the synthesis corresponding to the disconnection (b) is more simple and also the synthon $CO(OEt)_2$ (diethyl carbonate) is readily available.

Synthesis

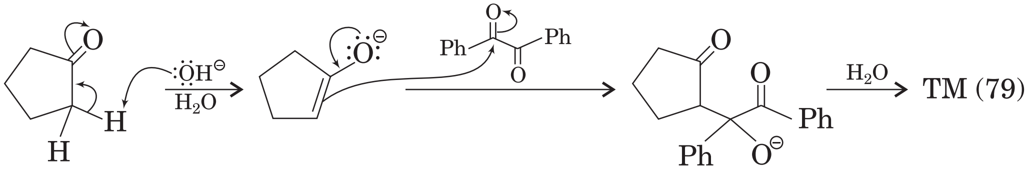


(f) *Retrosynthetic analysis*

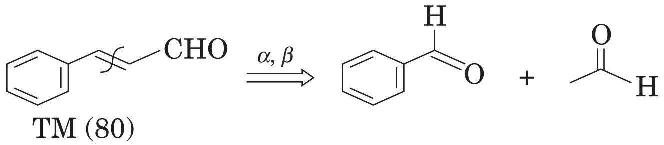


The disconnection (b) gives a very unstable and unknown synthon Ph—$\overset{\ominus}{C}$=O. The better disconnection is (a) which gives carbonyl compounds.

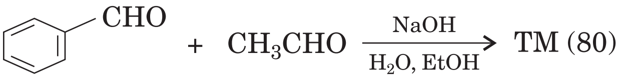
Synthesis



(g) *Retrosynthetic analysis*

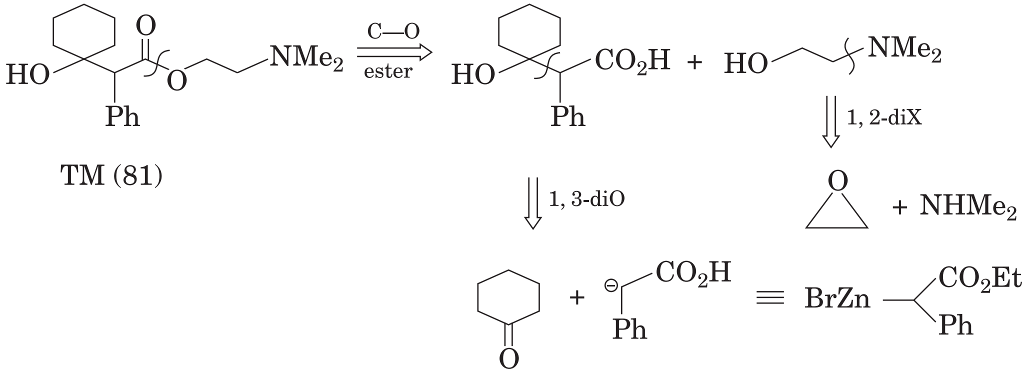


Synthesis



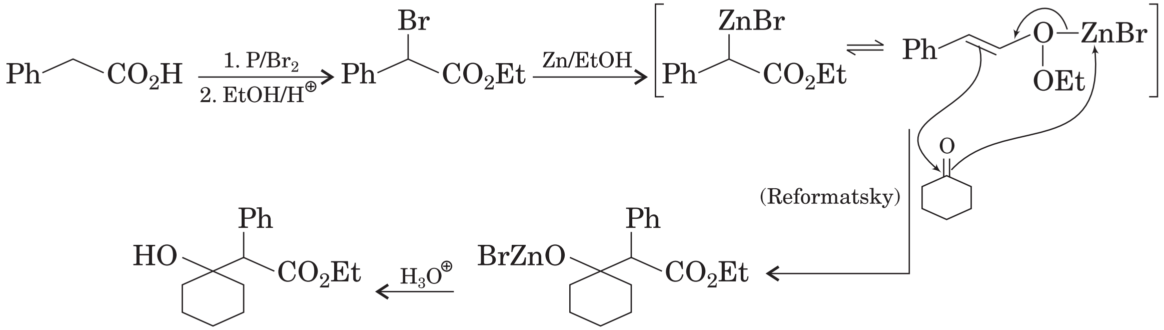
The synthesis is carried out in base (the *Claisen–Schmidt reaction*) with a large excess of benzaldehyde to minimize the self-condensation of acetaldehyde.

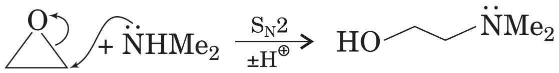
(h) *Retrosynthetic analysis*



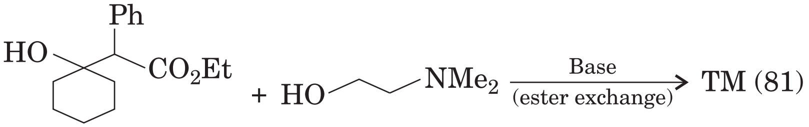
TM (81)

Synthesis

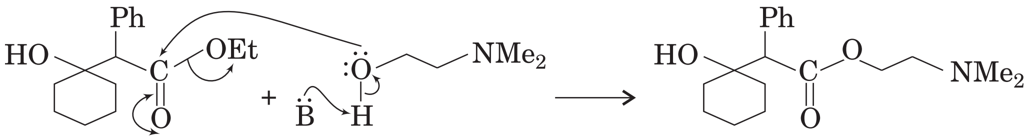




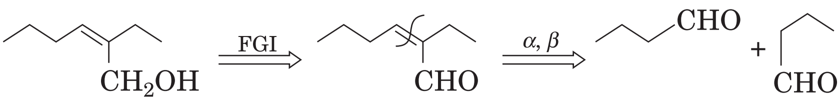
Then,



Mechanism



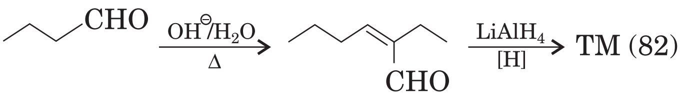
(i) *Retrosynthetic analysis*



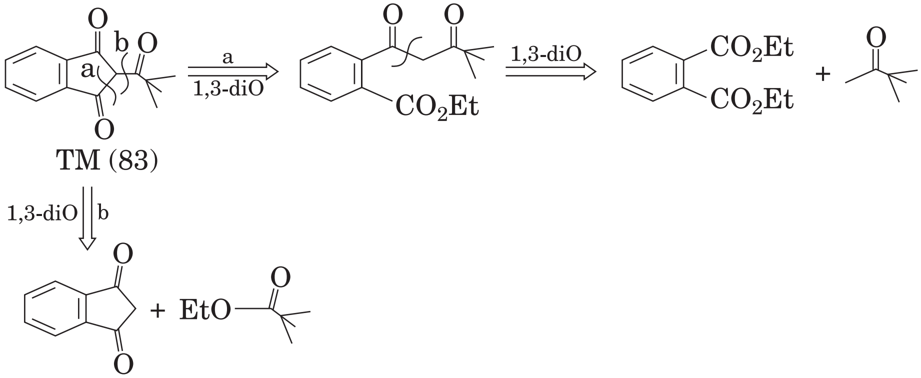
TM (82)

The two starting materials have the same skeleton. Therefore, it is better to carry out an aldol condensation using butanal and then to reduce the resulting aldehyde.

Synthesis

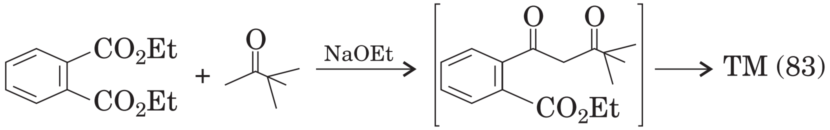


(j) *Retrosynthetic analysis*

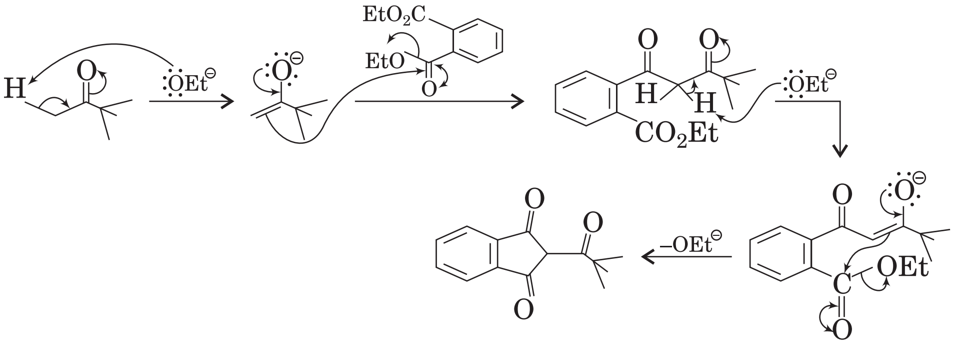


Since the disconnection (a) leads back to available starting materials, it is better than the disconnection (b).

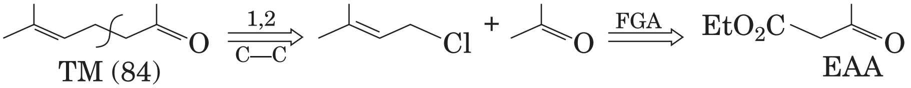
Synthesis



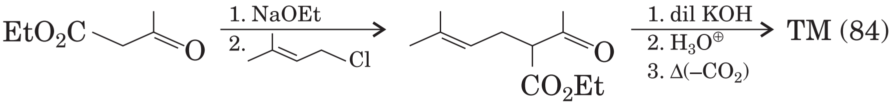
Mechanism:



(k) *Retrosynthetic analysis*

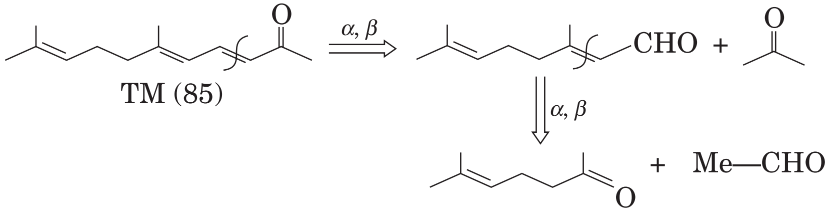


Synthesis



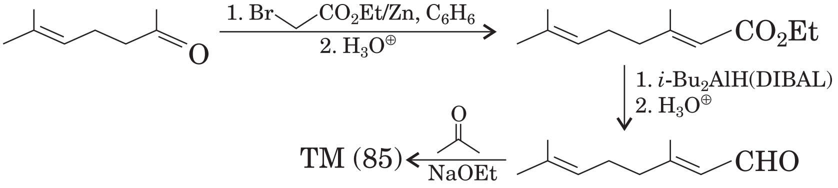
$Me_2C{=}CHCH_2Cl$ is a very good S_N2 substrate because the leaving group, Cl is located on a carbon atom that is both a primary and an allylic.

(l) *Retrosynthetic analysis*

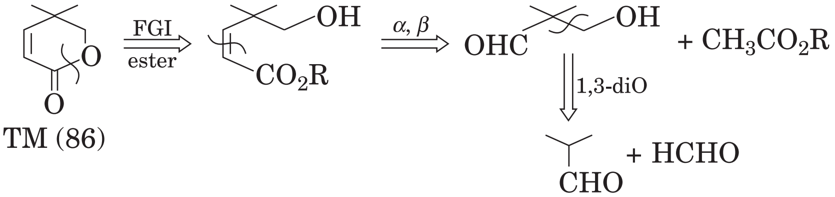


An aldol reaction involving the enolate of acetaldehyde and requiring to react with the ketone is unsuccessful because acetaldehyde itself is a very good electrophile. The first step in the forward synthesis is, therefore, to be carried out at the ester oxidation level using a Reformatsky reaction and the ester is subsequently converted to the aldehyde by reduction.

Synthesis

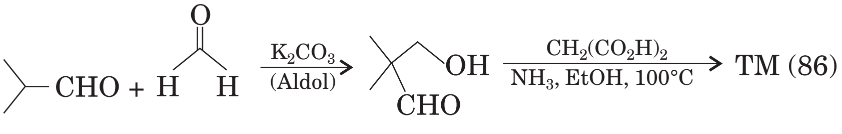


(m) *Retrosynthetic analysis*

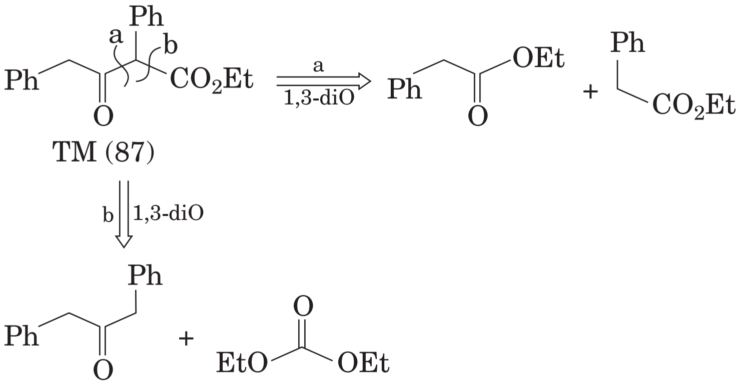


Synthesis

No control is needed in the first step because there is only one enolisable H atom on either aldehyde. If malonic acid is used for the second step, cyclisation and decarboxylation will take place spontaneously.



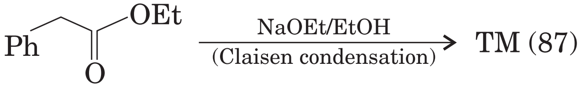
(n) *Retrosynthetic analysis*



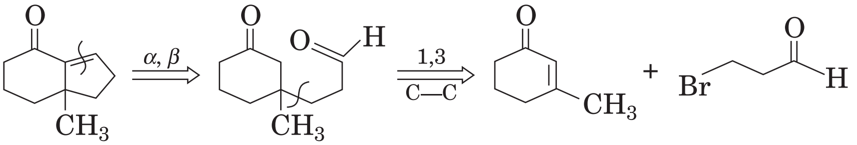
TM (87)

The disconnection (a) is more simple because only one starting material is required.

Synthesis



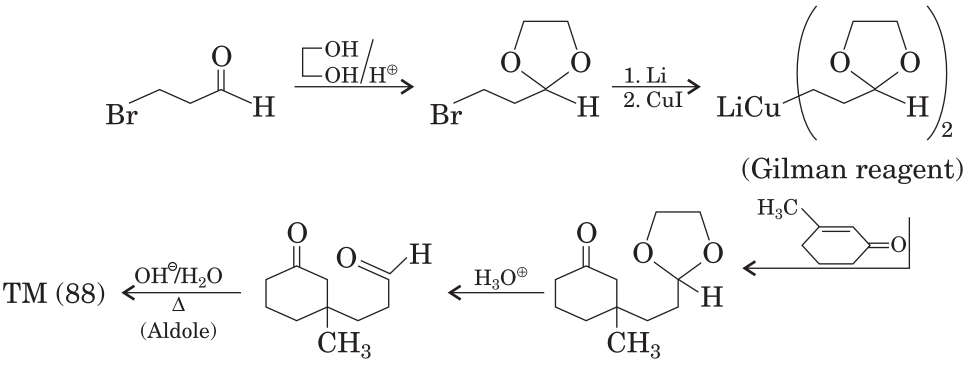
(o) *Retrosynthetic analysis*



TM (88)

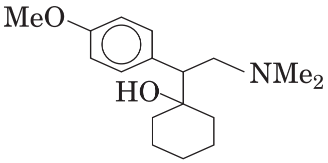
Synthesis

The side chain which is to be introduced as a nucleophile (for 1,4-addition) is expected to be an organocuprate reagent which in turn has to come from a halide *via* an organolithium compound. For successful preparation of the organolithium compound, the aldehyde group must be protected. Thus, the synthesis is carried out by the addition of the protected cuprate to the cyclohexenone, hydrolysis of the acetal to free the aldehyde group, and intramolecular aldol condensation.



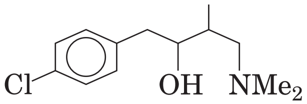
12. Give synthesis of each of the following target molecules with proper retrosynthetic analysis:

(a)



TM (89)
Venlafaxin
(an antidepressant)

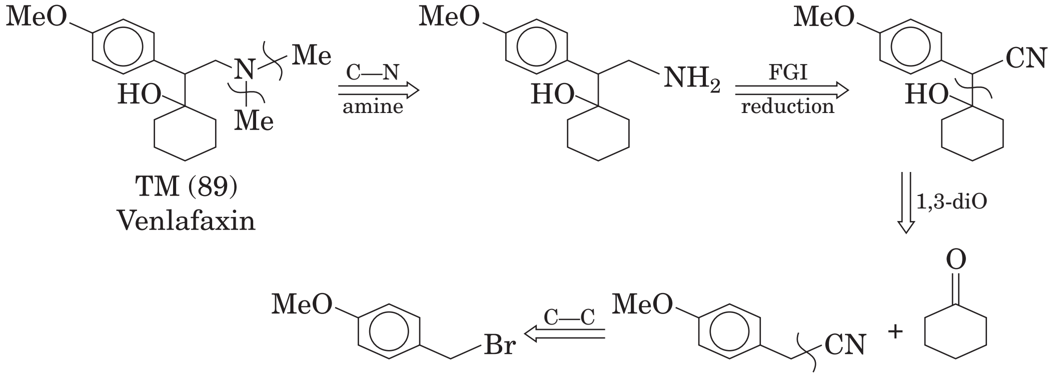
(b)



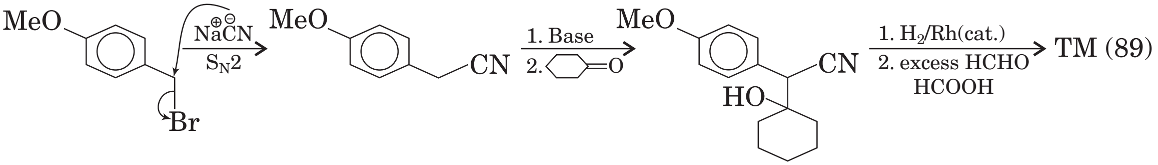
TM (90)
Clobutinol (an antitussive)

Solution

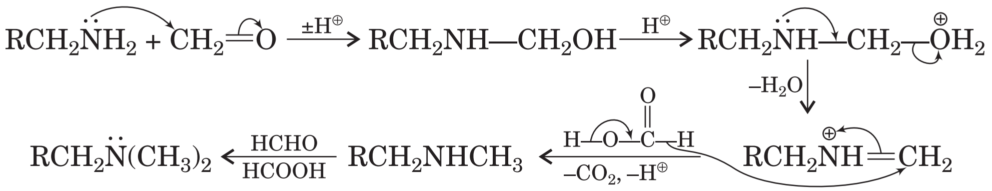
(a) *Retrosynthetic analysis*



Synthesis



Mechanism of conversion of R—CH$_2$NH$_2$ to RCH$_2$NMe$_2$

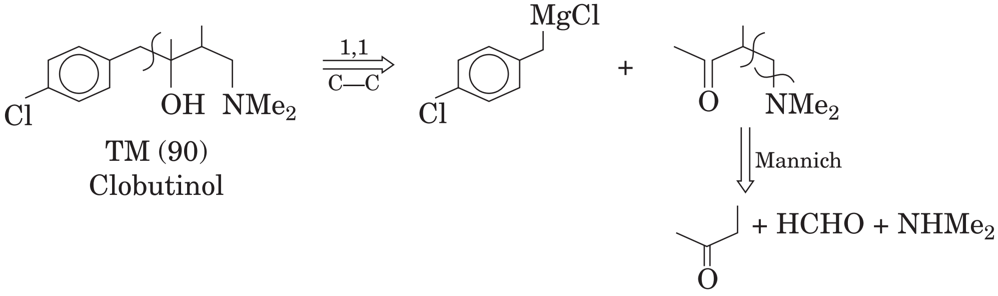


$$RCH_2\ddot{N}H_2 + CH_2{=}O \xrightarrow{\pm H^{\oplus}} RCH_2NH{-}CH_2OH \xrightarrow{H^{\oplus}} RCH_2\ddot{N}H{-}CH_2{-}\overset{\oplus}{O}H_2$$

$$\xrightarrow{-H_2O} RCH_2\overset{\oplus}{N}H{=}CH_2$$

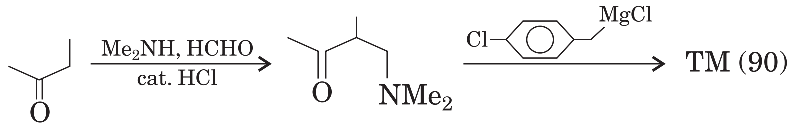
$$RCH_2\overset{\oplus}{N}H{=}CH_2 \xrightarrow[-CO_2,\ -H^{\oplus}]{H{-}O{-}\overset{O}{\overset{\|}{C}}{-}H} RCH_2NHCH_3 \xrightarrow[HCOOH]{HCHO} RCH_2\ddot{N}(CH_3)_2$$

(b) *Retrosynthetic analysis*



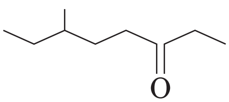
TM (90)
Clobutinol

Synthesis



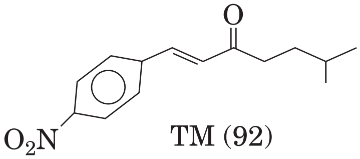
13. Propose a synthesis for each of the following compounds with proper retrosynthetic analysis:

(a)



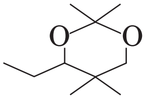
TM (91)

(b)



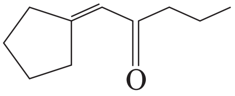
TM (92)

(c)



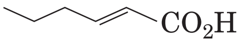
TM (93)

(d)



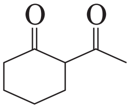
TM (94)

(e)



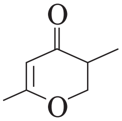
TM (95)

(f)



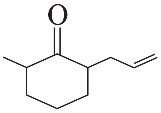
TM (96)

(g)



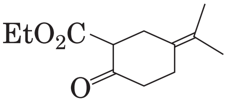
TM (97)

(h)



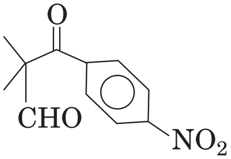
TM (98)

(i)



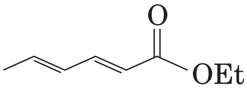
TM (99)

(j)



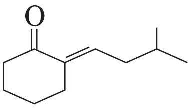
TM (100)

(k)



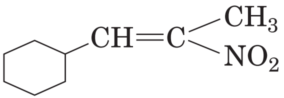
TM (101)

(l)



TM (102)

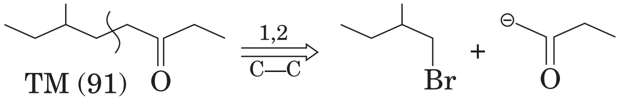
(m)



TM (103)

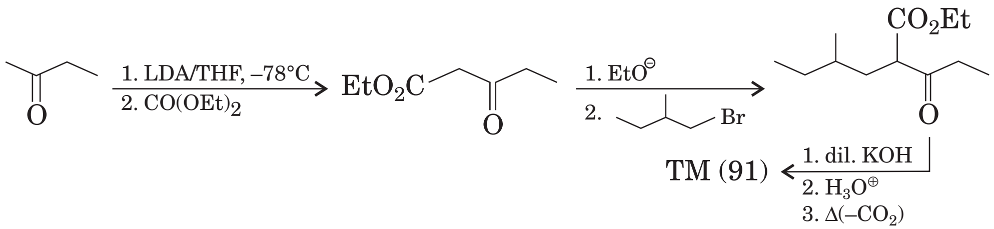
Solution

(a) *Retrosynthetic analysis*

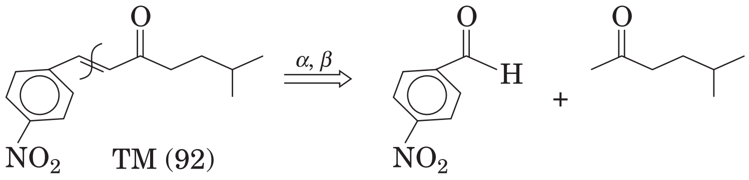


The synthesis requires a specific enol (ate) equivalent for 2-butanone.

Synthesis

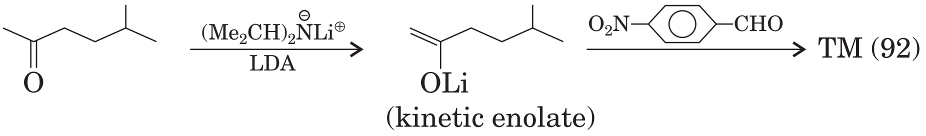


(b) *Retrosynthetic analysis*

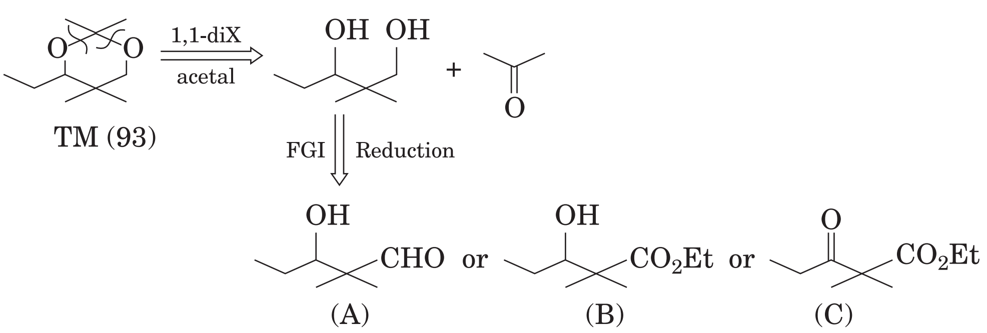


Synthesis

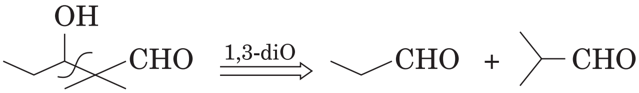
This synthesis requires one enolate from the unsymmetrical ketone, and therefore, we need regioslectivity. The problem can be solved by using lithium enolate, a silyl enol ether, or a compound with an extra ester group.



(c) *Retrosynthetic analysis*



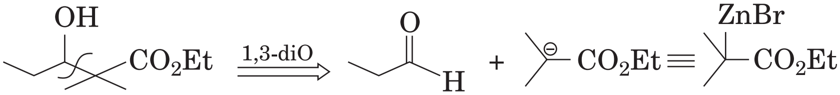
Disconnection of (A):



(A)

Since the synthesis of (A) requires a crossed Aldol reaction, it should be avoided and this is because a number of products is expected to be formed.

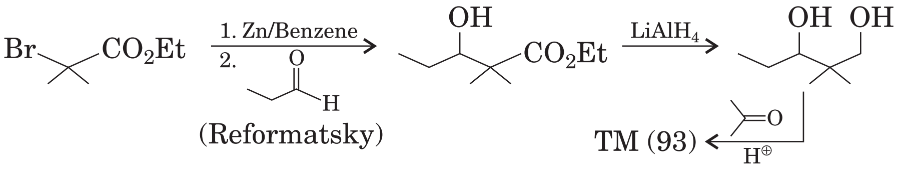
Disconnection of (B):



(B)

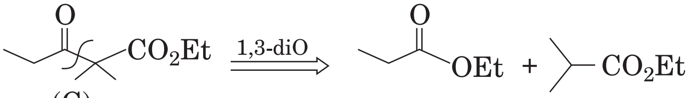
Synthesis of compound (B) requires a specific enol equivalent (Reformatsky reagent).

Synthesis

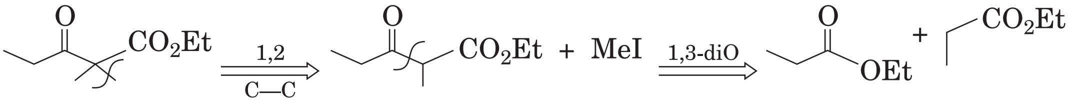


Disconnection of (C):

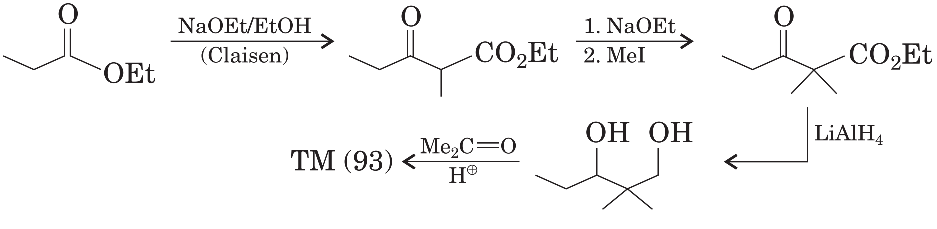
Direct disconnection of the β-ketoester (C) suggest a crossed Claisen condensation which is, therefore, not useful. However, if one of the methyl group is disconnected first, a very simplified process results because a self-condensation of ethyl propanoate can be used.



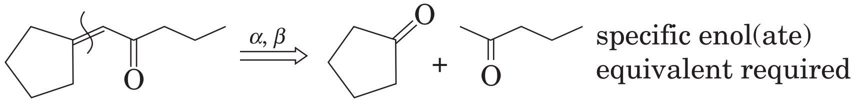
(C)



Synthesis



(d) *Retrosynthetic analysis*

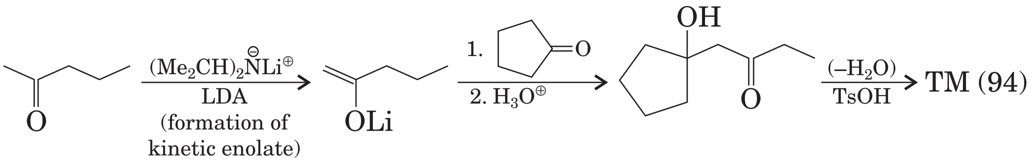


TM (94)

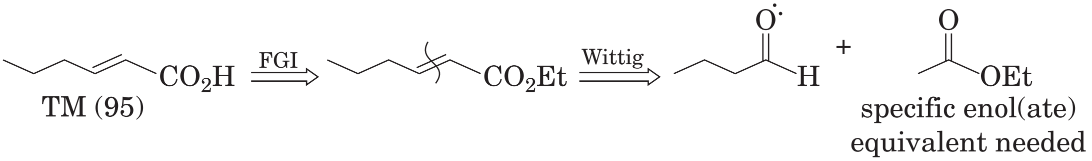
The synthesis involves a crossed aldol condensation between two ketones. Therefore, we need chemoselectivity.

Also, the synthesis requires one enolate from the unsymmetrical ketone and therefore, we need regioselectivity too. The problem can be solved by using a lithium enolate, a silyl enol ether, or a compound containing an additional ester group.

Synthesis

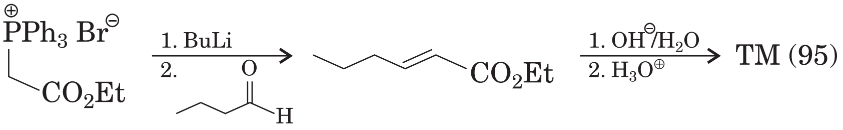


(e) *Retrosynthetic analysis*

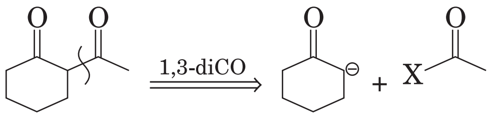


TM (95)

Synthesis



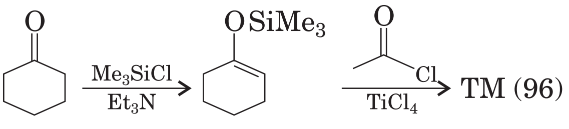
(f) *Retrosynthetic analysis*



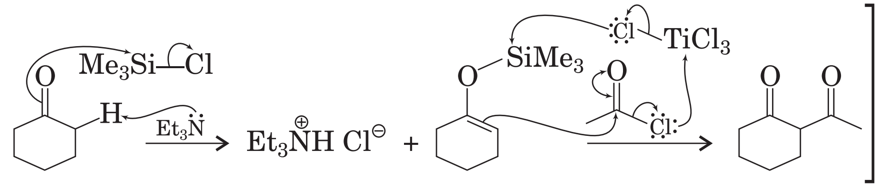
TM (96)

The synthesis requires a specific enol(ate) equivalent for cyclohexanone.

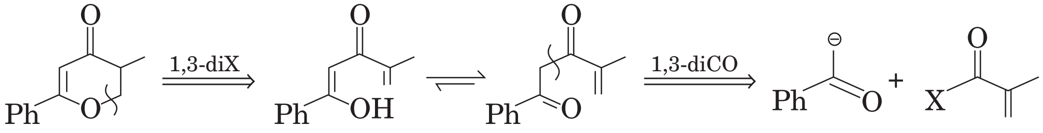
Synthesis



Mechanism:



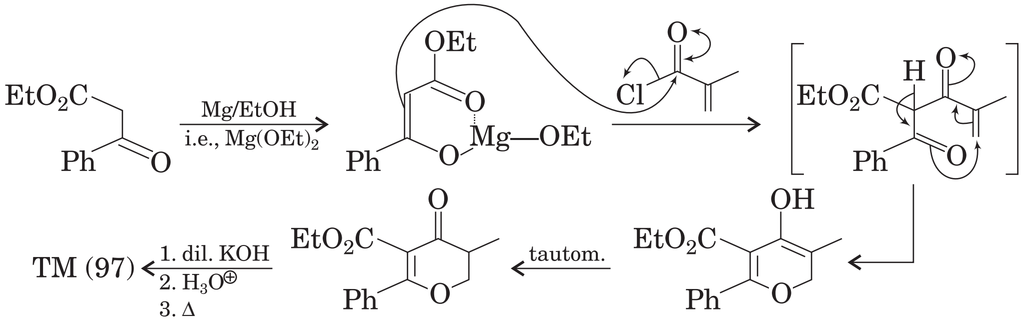
(g) *Retrosynthetic analysis*



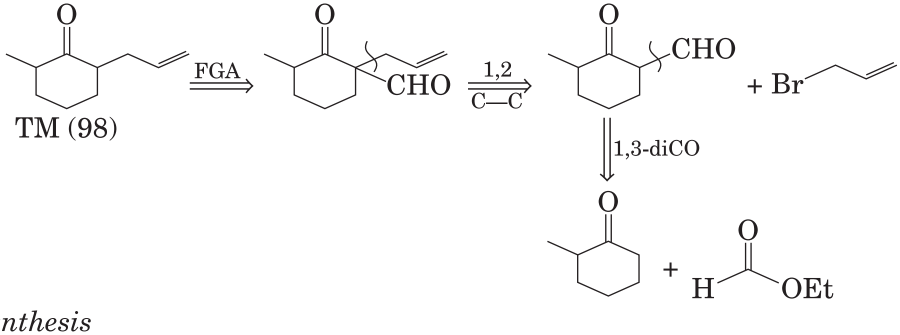
TM (97)

The synthesis requires the use of a specific enol equivalent of acetophenone. Sodium or potassium enolate acylate on oxygen. It is, therefore, used as magnesium enolate because in this molecule the oxygen atoms are chelated by Mg, leaving carbon free to react.

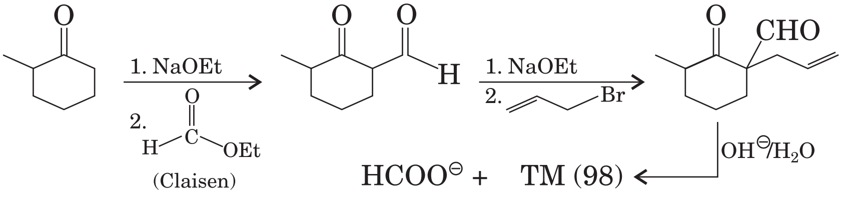
Synthesis



(h) *Retrosynthetic analysis*

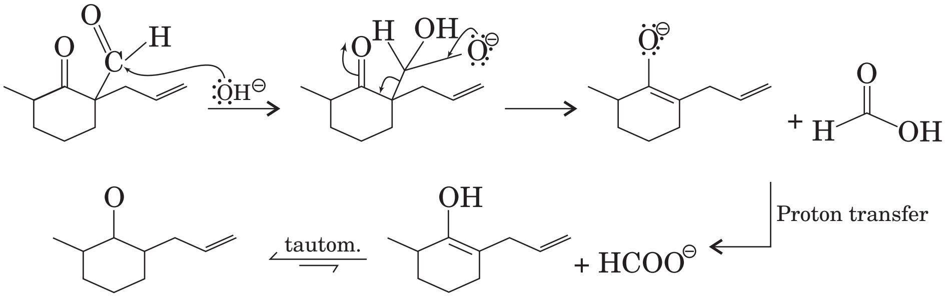


Synthesis

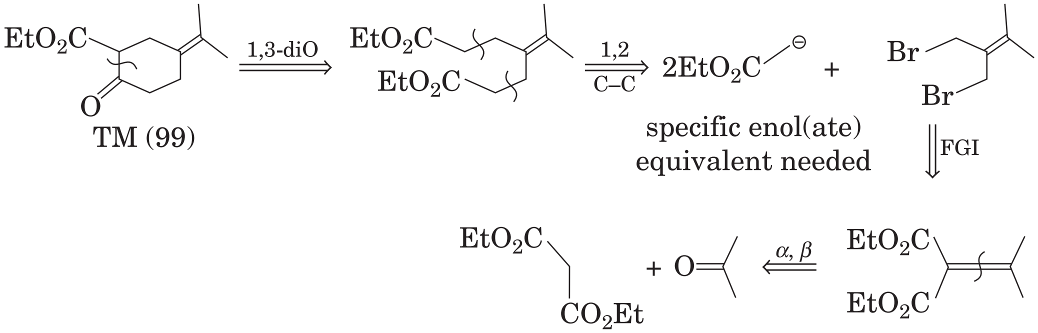


The first reaction (introduction of a –CHO group) is regioselective because the product can itself enolise in the basic reaction medium to form a stable delocalised enolate. This drives the equilibrium over and would not be possible with the other product containing no reactive methylene hydrogen.

Mechanism of –CHO removal:

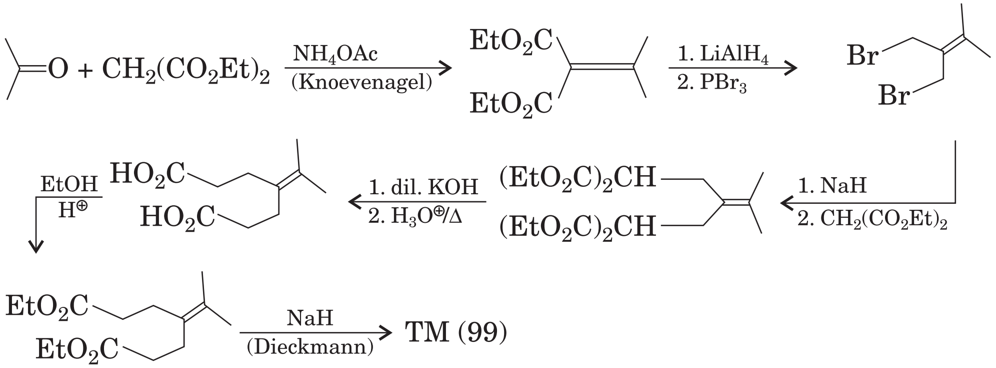


(i) *Retrosynthetic analysis*

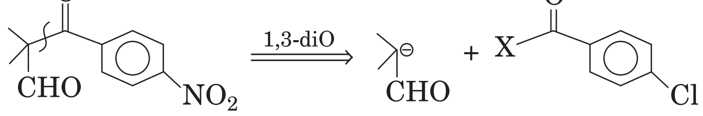


TM (99)

Synthesis



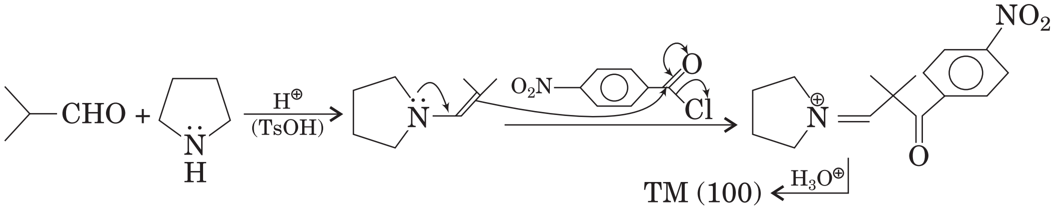
(j) *Retrosynthetic analysis*



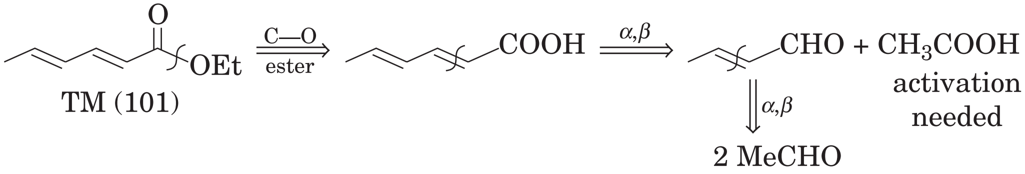
TM (100)

Synthesis

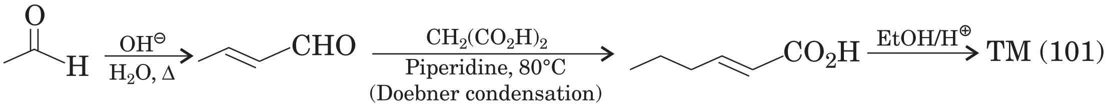
The reaction may be carried out easily through the formation of an enamine of the aldehyde.



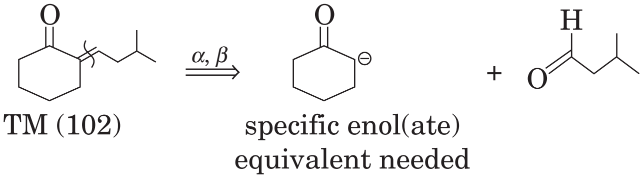
(k) *Retrosynthetic analysis*



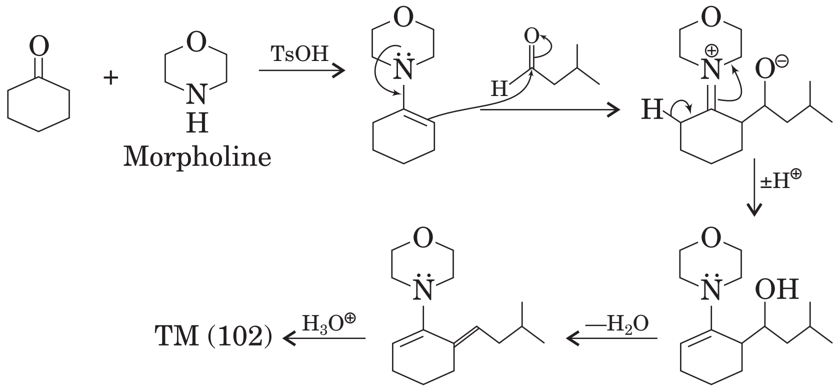
Synthesis



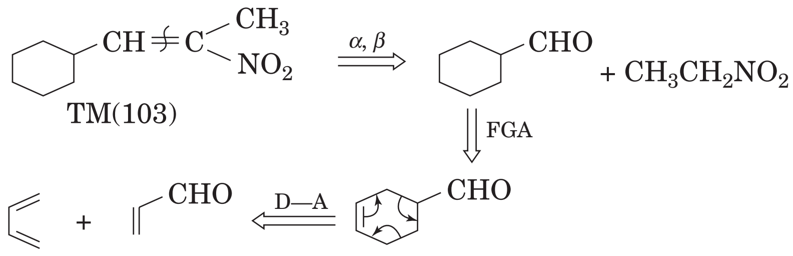
(l) *Retrosynthetic analysis*



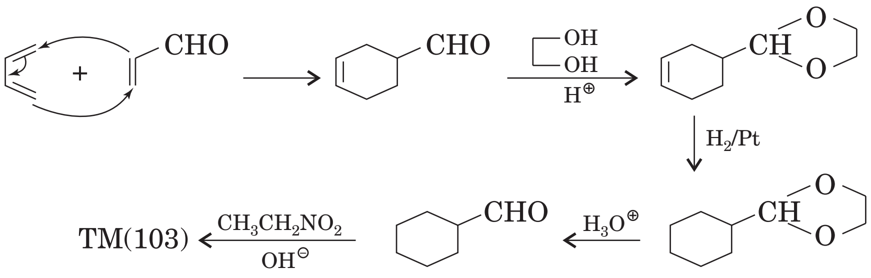
Synthesis



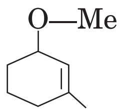
(m) *Retrosynthetic analysis*



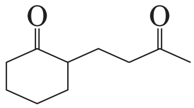
Synthesis



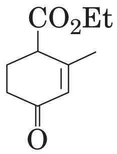
14. Using disconnection approach design a convenient sythesis for each of the following compounds:

(a)


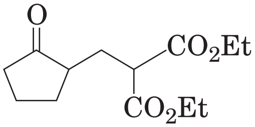
TM (104)

(b)


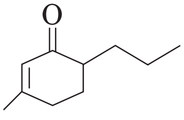
TM (105)

(c)


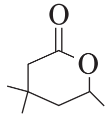
TM (106)

(d)


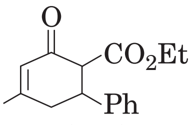
TM (107)

(e)


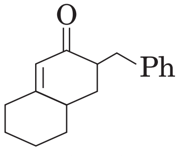
TM (108)

(f)


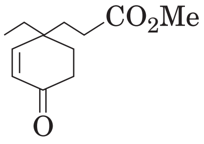
TM (109)

(g)


TM (110)

(h)


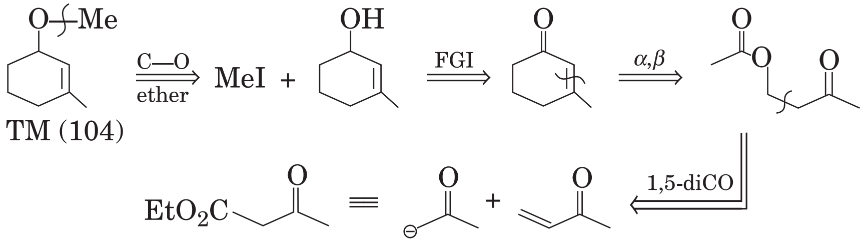
TM (111)

(i)


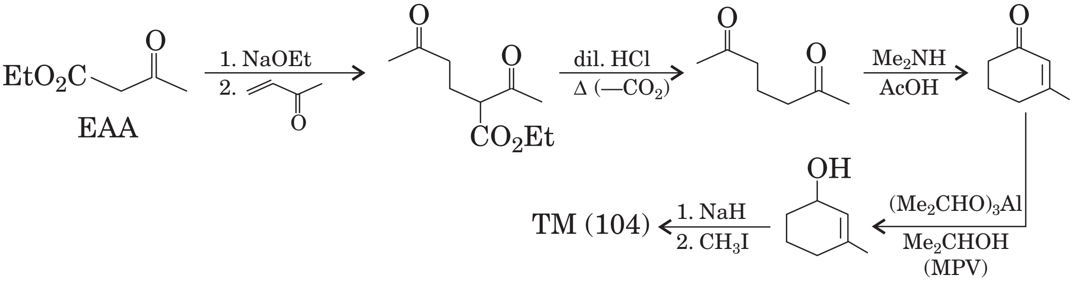
TM (112)

Solution

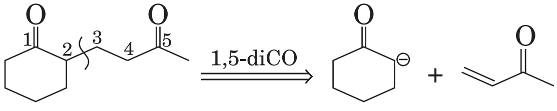
(a) *Retrosynthetic analysis*



Synthesis



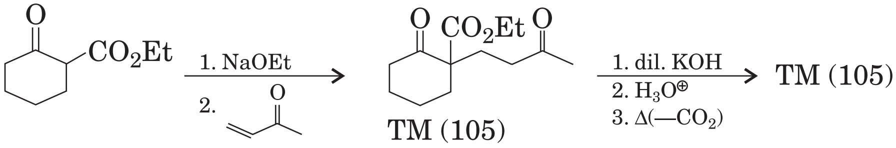
(b) *Retrosynthetic analysis*



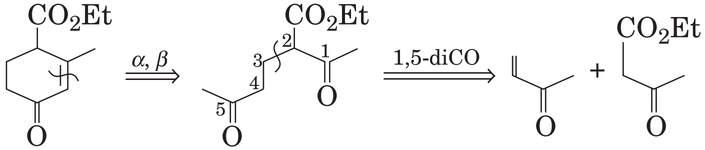
TM (105)

A specific enol(ate) equivalent is required for cyclopentanone. This may be obtained by the addition of the activating group –CO_2Et.

Synthesis



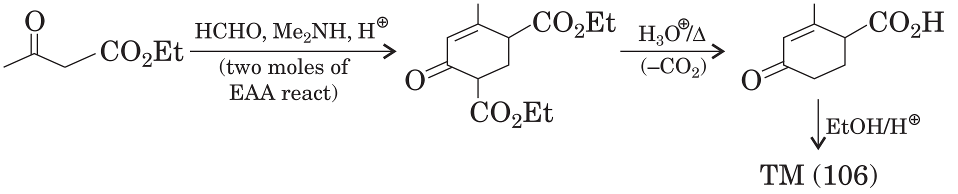
(c) *Retrosynthetic analysis*



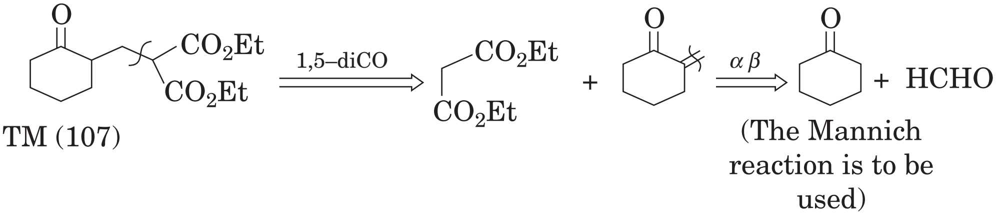
TM (106)

If an activating group (–CO_2Et) is added to the acetone molecule, our starting materials will be two molecules of ethyl acetoacetate and one molecule of formaldehyde. This ester can actually be made in two steps without having to alkylate the Mannich base.

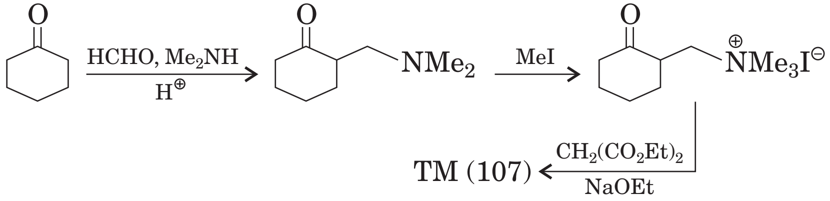
Synthesis



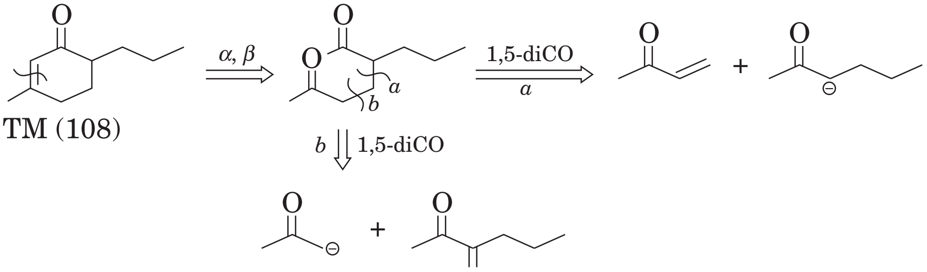
(d) *Retrosynthetic analysis*



Synthesis

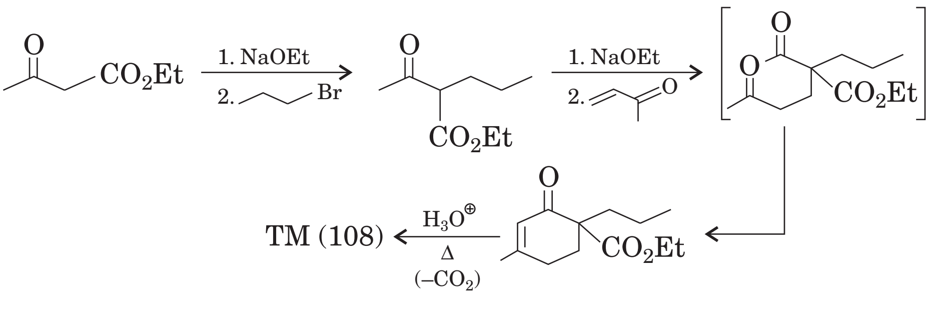


(e) *Retrosynthetic analysis*

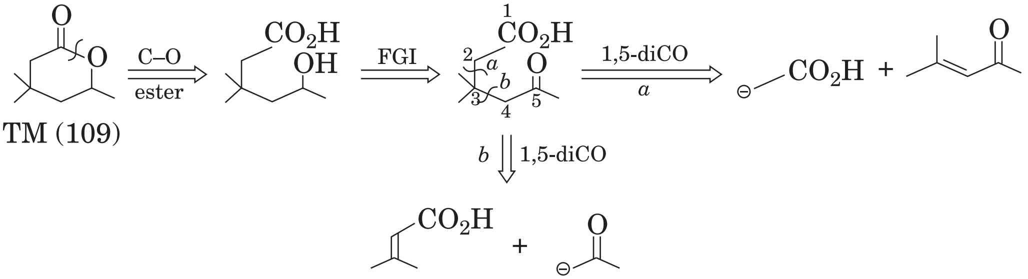


The Michael disconnection (a) is better than (b), since in that case, the $-CO_2Et$ control group can be used both for alkylation (to add a propyl group) and for conjugate addition.

Synthesis

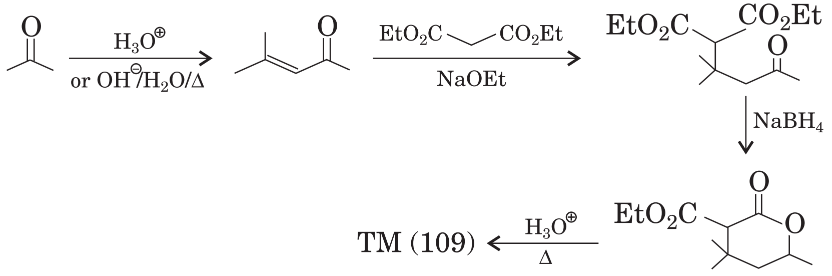


(f) *Retrosynthetic analysis*

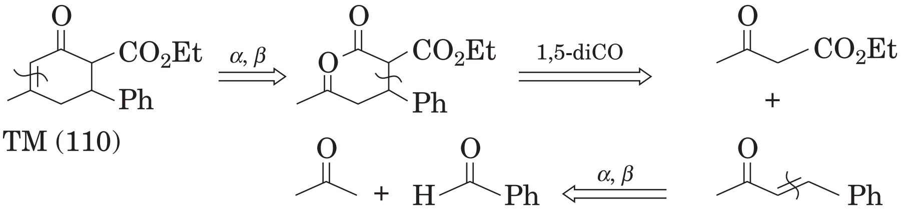

TM (109)

Synthesis based on either the disconnection (a) or the disconnection (b) is expected to be fruitful. However, the disconnection (a) is better because the enone starting material (a dimer of acetone) can be prepared very easily. A specific enol(ate) equivalent is needed and malonate is the best one. Also, there is no problem with chemoselective reduction as $NaBH_4$ reduces ketones but not esters. The hydroxy-ester cyclizes during work-up to give the lactone (109).

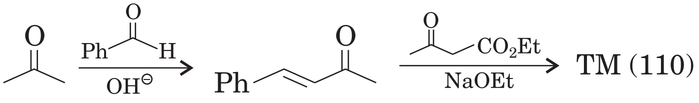
Synthesis


TM (109)

(g) *Retrosynthetic analysis*

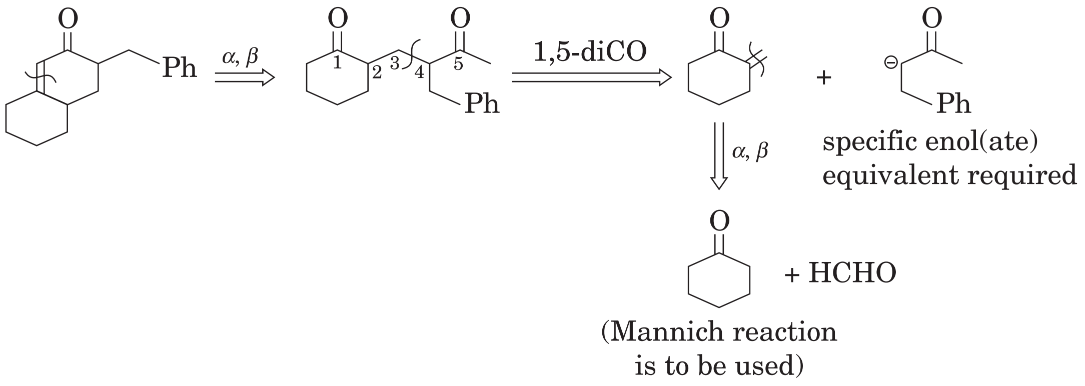

TM (110)

Synthesis


TM (110)

This sequence of Michael addition and cyclisation is known as *Robison annulation* since it makes a ring.

(h) *Retrosynthetic analysis*

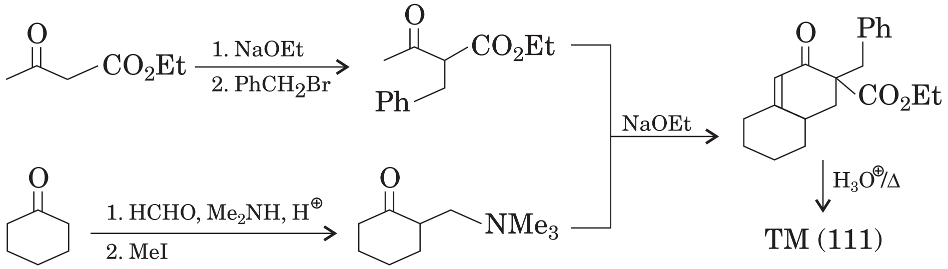


specific enol(ate) equivalent required

(Mannich reaction is to be used)

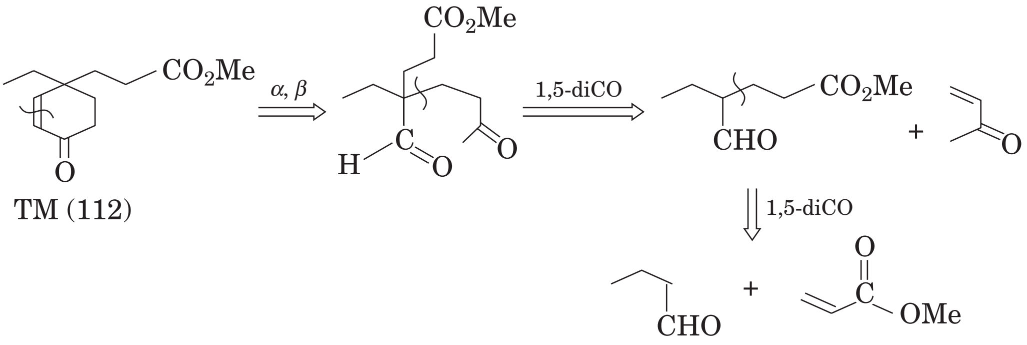
An activating group like –CO_2Et is to be added to control the Mannich reaction leading to a 1,5-diketone. The specific enol(ate) equivalent is to be made by alkylation of ethyl acetoacetate (EAA).

Synthesis



TM (111)

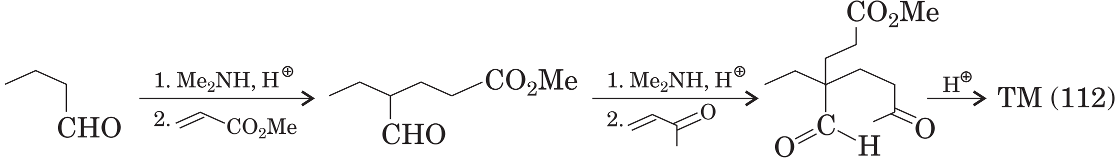
(i) *Retrosynthetic analysis*



TM (112)

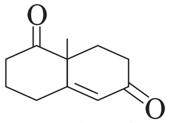
Both of the Michael addition require an activation group. However, it cannot be a –CO_2R group because the reaction corresponding to second 1,5-diCO disconnection is not possible. Therefore, activation is done by forming an enamine.

Synthesis



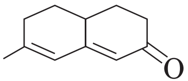
15. Suggest a synthesis for each of the following compounds with proper retrosynthetic analysis:

(a)



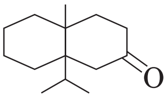
TM (113)

(b)



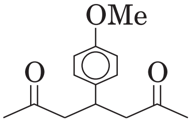
TM (114)

(c)



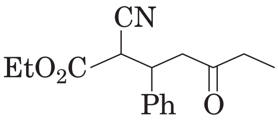
TM (115)

(d)



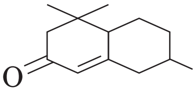
TM (116)

(e)



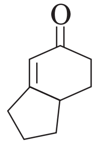
TM (117)

(f)



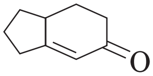
TM (118)

(g)



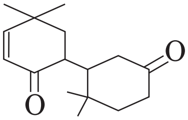
TM (119)

(h)



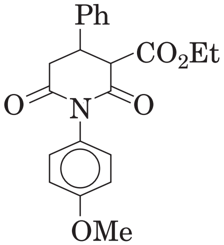
TM (120)

(i)



TM (121)

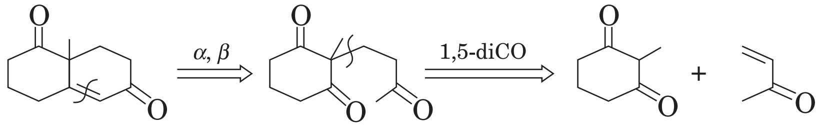
(j)



TM (122)

Solution

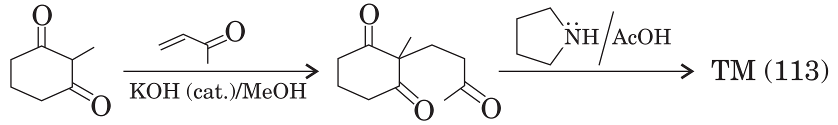
(a) *Retrosynthetic analysis*



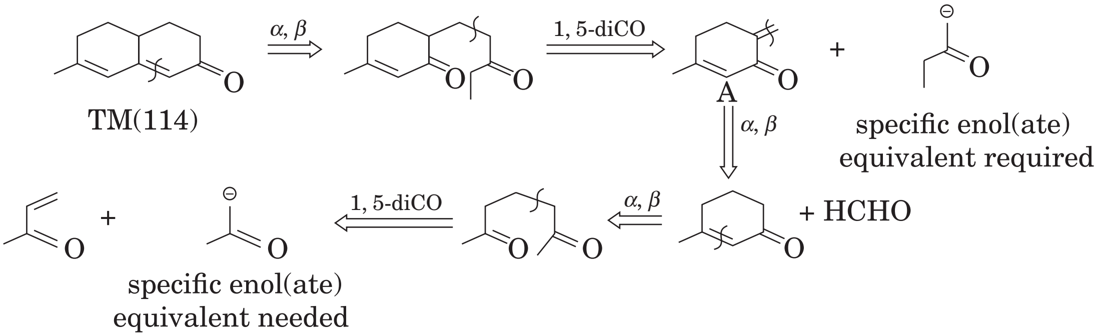
TM (113)

An α,β-disconnection on the target molecule results in formation of a 1,5-diketone. A very good disconnection for this triketone is at the ring-chain junction to give a symmetrical diketone with in-built activation. A catalytic amount of base is required for the Michael addition as position C-4 in the addition product is blocked and cannot enolise. In the next step, controlled aldol condensation is better to arrest the linear aldol condensation.

Synthesis

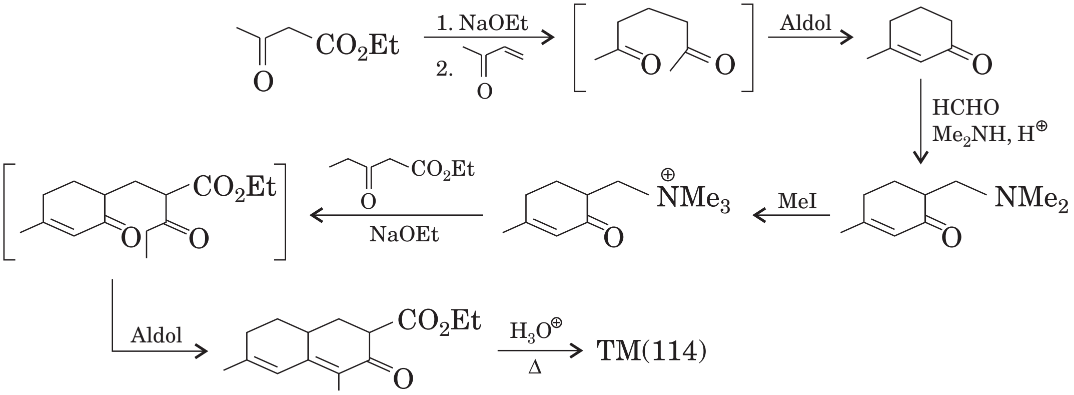


(b) *Retrosynthetic analysis*

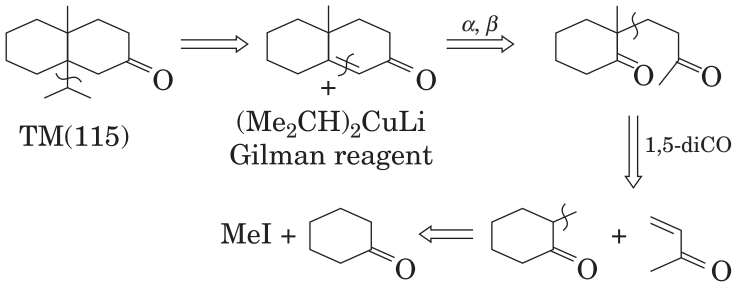

TM(114)
α, β
1, 5-diCO
A
α, β
specific enol(ate) equivalent required
+ HCHO
α, β
1, 5-diCO
specific enol(ate) equivalent needed

The Michael addition on A could in principle take place at the β-position of either double bond. However, the unsubstituted position out of the ring is relatively much reactive than the disubstituted position in the ring.

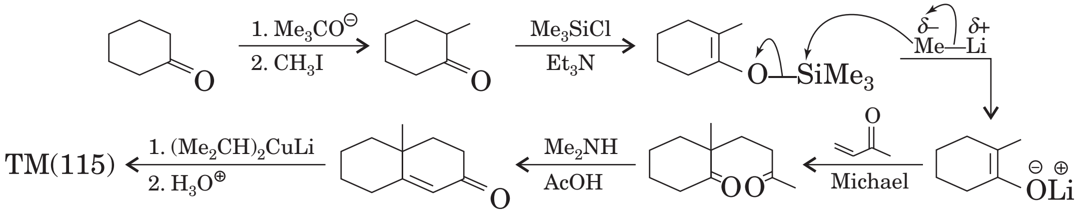
Synthesis



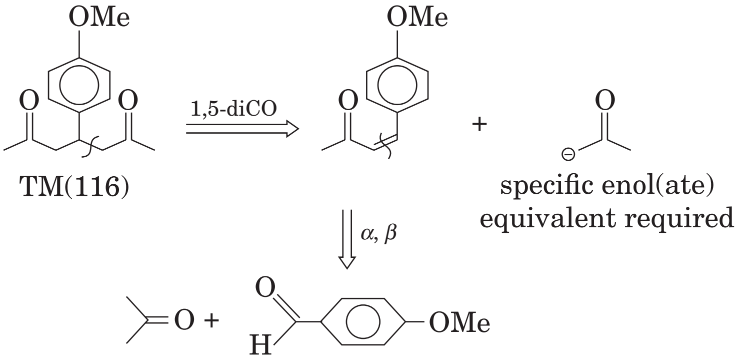
(c) *Retrosynthetic analysis*



Synthesis

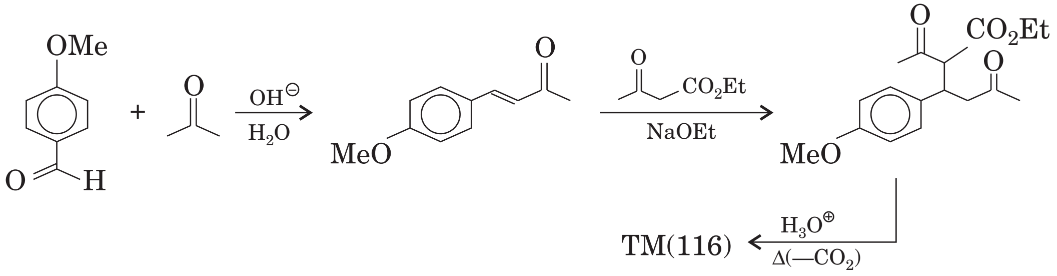


(d) *Retrosynthetic analysis*

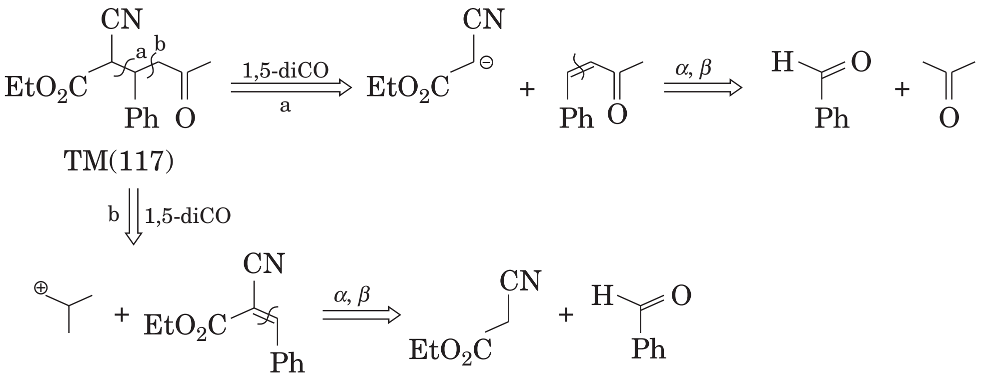


The reaction is best carried out by using ethyl acetoacetate as the specific enol(ate) equivalent.

Synthesis

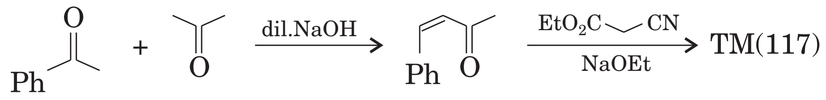


(e) *Retrosynthetic analysis*

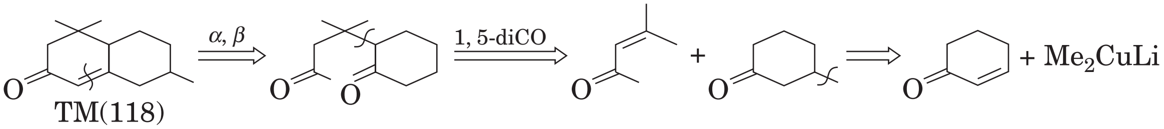


Both of these two possible disconnections are acceptable and both of them get back to the same three starting materials. However, the disconnection (a) is more favourable because it uses a Michael addition with a stable anion (resonance stabilized by –CN and CO_2Et groups).

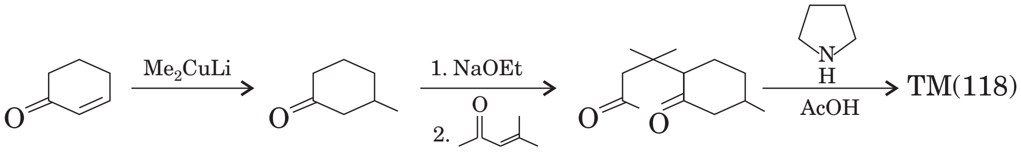
Synthesis



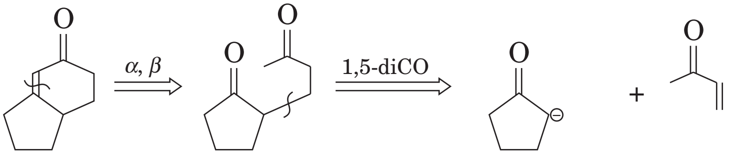
(f) *Retrosynthetic analysis*



Synthesis



(g) *Retrosynthetic analysis*

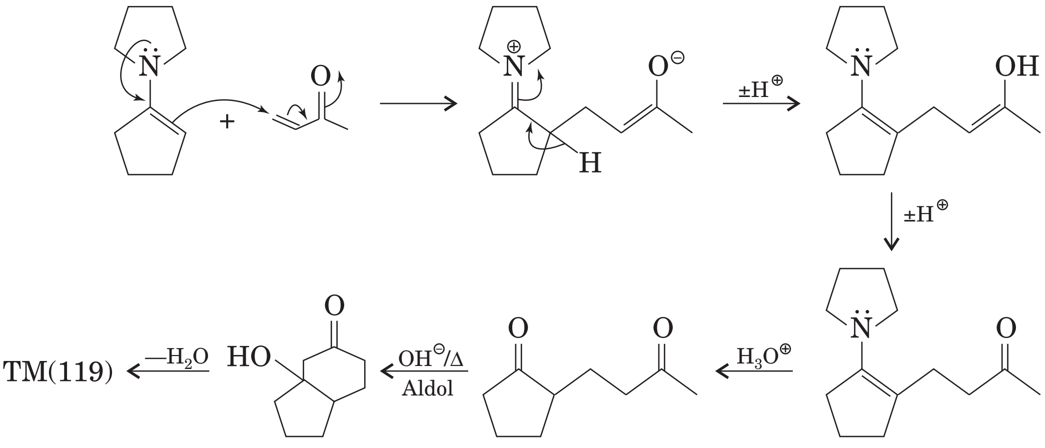


TM(119)

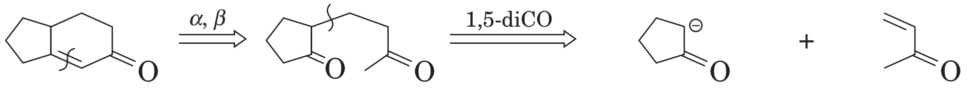
specific enol(ate)
equivalent needed

Recall that enamines react with electrophiles in the same way that enolate ions do. Also, enamines add cleanly in Michael fashion (1,4-addition) to an *α*,*β*-unsaturated carbonyl system.

Synthesis



(h) *Retrosynthetic analysis*



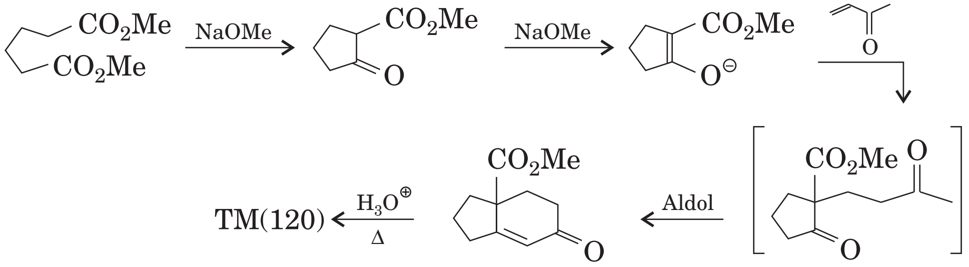
TM(120)

specific enol(ate)
equivalent needed

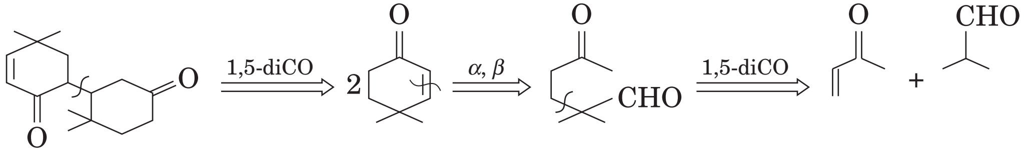
The enolate must have an activating group to ensure both enolisation at that site and Michael rather than direct addition to the α,β-unsaturated ketone.

Synthesis

The keto-ester for the required enolate can be easily prepared by the Dieckmann condensation involving dimethyl adipate.



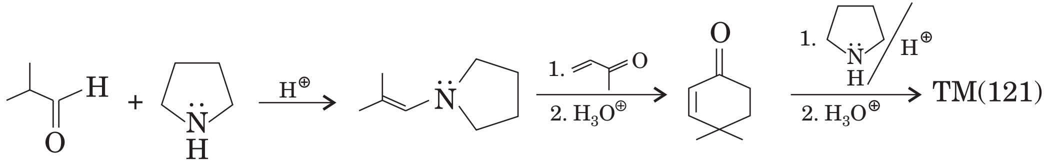
(i) *Retrosynthetic analysis*



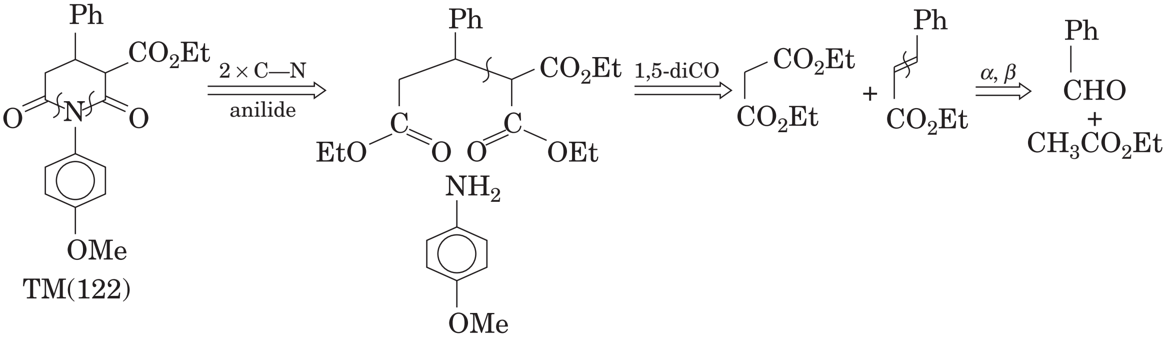
TM(121)

The synthesis is carried out by using enamine because there is no room for an activating group.

Synthesis



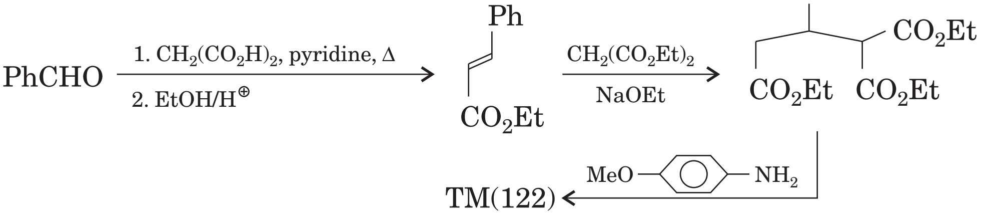
(j) *Retrosynthetic analysis*



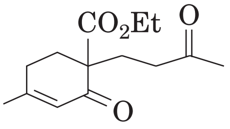
TM(122)

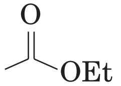
In practice, the unsaturated ester is prepared condensation followed by esterification.

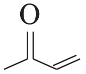
Synthesis



16. Show with proper retrosynthetic analysis that the compound (123) can be synthesized by using very simple starting materials like ethyl acetate and methyl vinyl ketone (MVK).

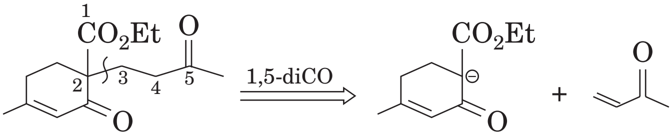

TM(123)


Ethyl acetate


MVK

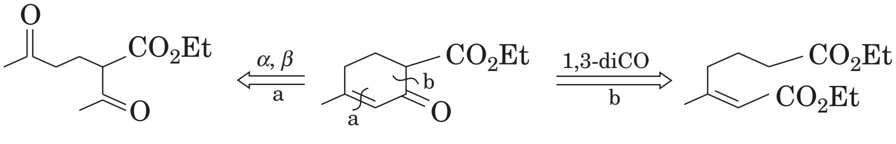
Solution

Retrosynthetic analysis

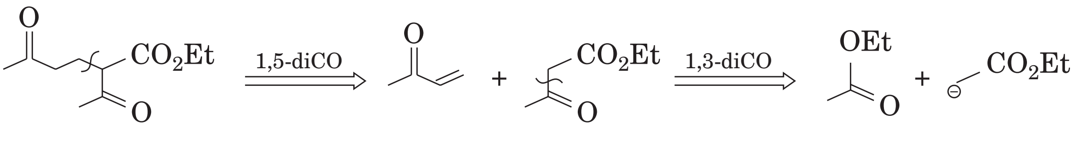


TM(123)

This disconnection is a good one as it trims off the side chain from the ring and also, it uses a Michael addition with a stable anion. Now, the keto-ester can be disconnected in two ways (1,3-diCO disconnection or disconnection of the α,β-double bond, i.e., α,β-disconnection).

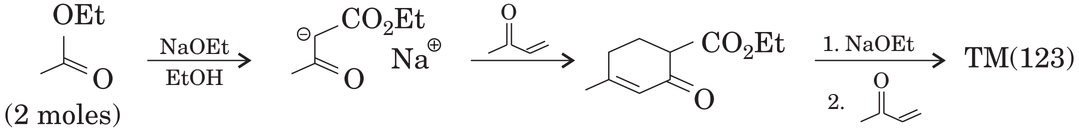


The disconnection (b) requires formation of an α-β-unsaturated carbonyl system with one particular geometric isomer (*cis*), and therefore, it is not a good one. The disconnection (a), on the other hand, reveals a new 1,5-diCO relationship. Disconnecting this at the branch point leads to another readily available enone and a β-keto-ester (EAA) which can easily be prepared from ethyl acetate (CH_3CO_2Et) by Claisen condensation.

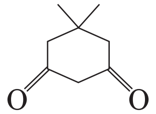


The synthesis of the target molecule, therefore, requires two very simple compounds such as ethyl acetate and methyl vinyl ketone.

Synthesis



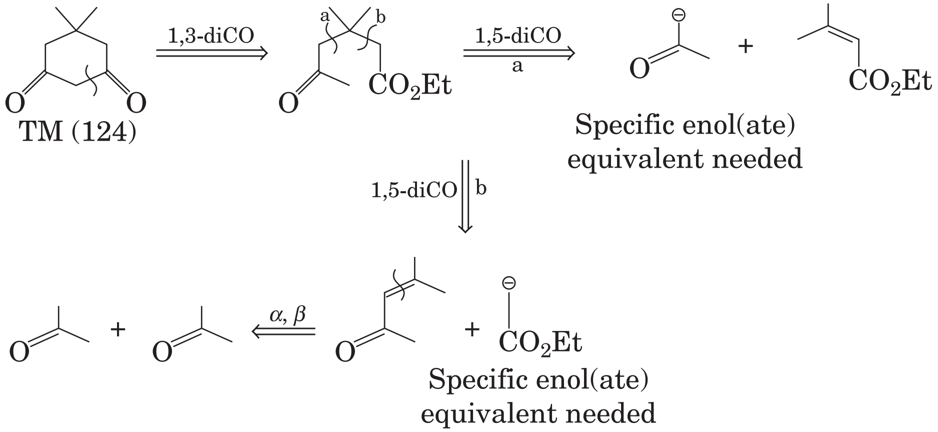
17. Give two possible syntheses of dimedone (5,5-dimethylcyclohexane-1,3-dione) with proper retrosynthetic analysis:



TM (124)
(Dimedone)

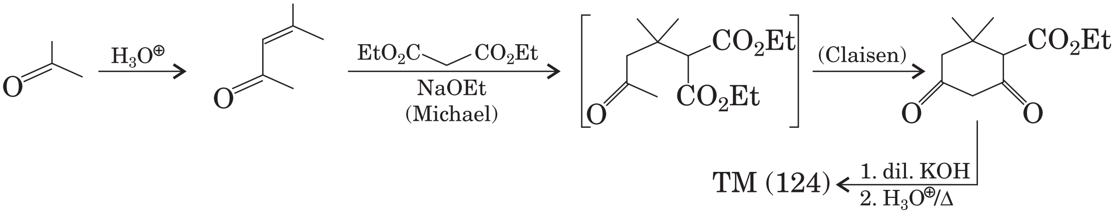
Solution Synthesis of dimedone may be carried out by using the following two methods (I and II):

Retrosynthetic analysis (I)

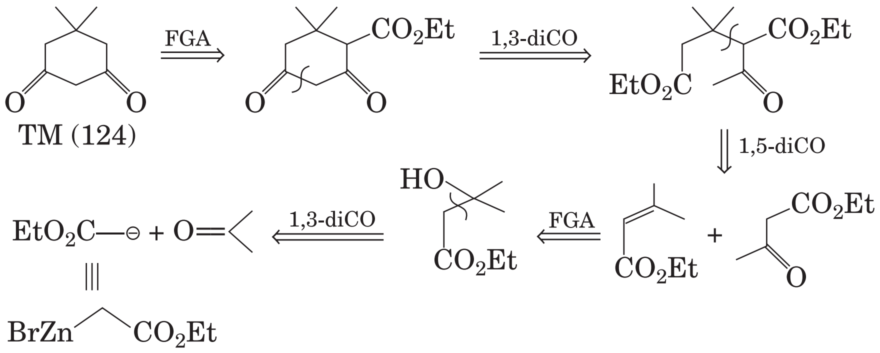

O
O
TM (124)
1,3-diCO
a
b
CO2Et
1,5-diCO
a
+
CO2Et
Specific enol(ate) equivalent needed
1,5-diCO
b
+
α, β
+
CO2Et
Specific enol(ate) equivalent needed

Either disconnection (a) or (b) would lead to a good synthesis of dimedone. However, the disconnection (b) is better because both starting materials are readily available. The enone is actually the dimer of acetone obtained by Aldol condensation.

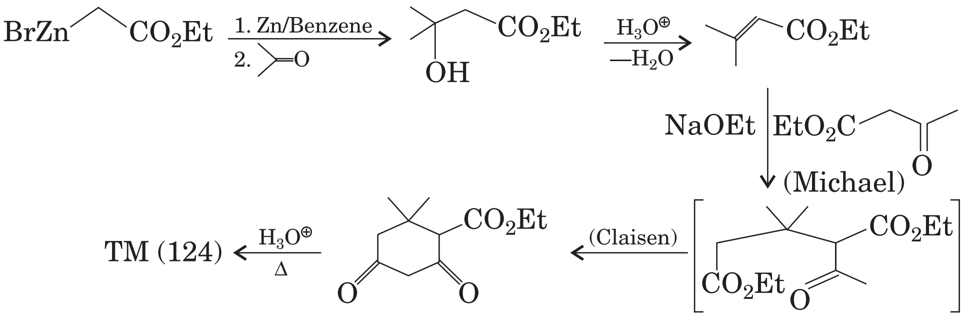
Synthesis (*I*)



Retrosynthetic analysis (II)

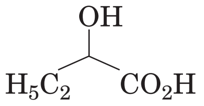


Synthesis (II)

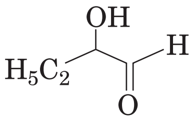


Umpolung syntheses

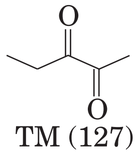
18. Suggest a synthesis for each of the following target molecules (1,2-dioxygen systems) with retrosynthetic analysis involving illogical disconnections:

(a) 

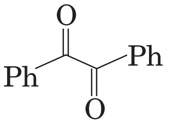
TM (125)

(b) 

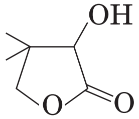
TM (126)

(c) 

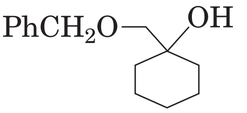
TM (127)

(d) 

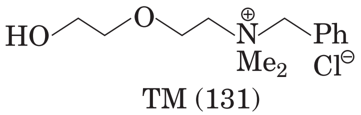
TM (128)

(e) 

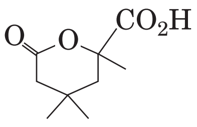
TM (129)

(f) 

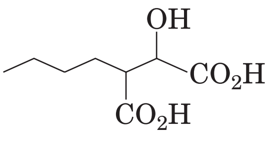
TM (130)

(g) 

TM (131)

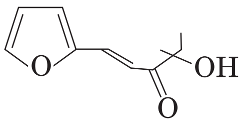
(h) 

TM (132)

(i) 

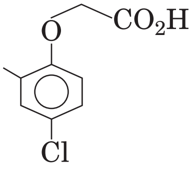
TM (133)

(j)



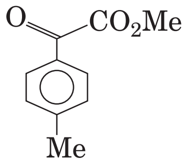
TM (134)

(k)



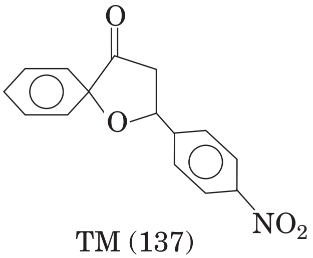
TM (135)

(l)



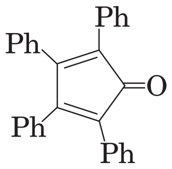
TM (136)

(m)



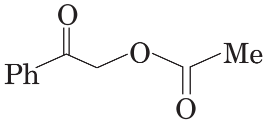
TM (137)

(n)



TM (138)

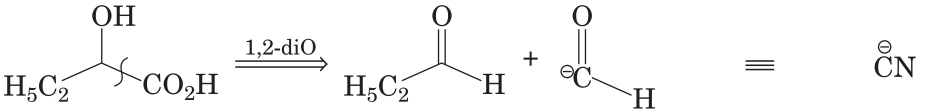
(o)



TM (139)

Solution

(a) *Retrosynthetic analysis*

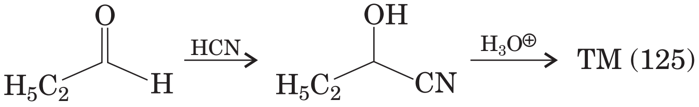


TM (125)

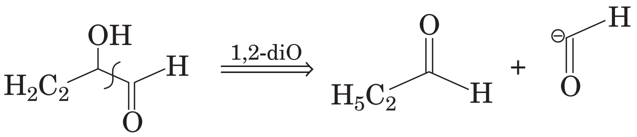
Illogical or umpolung synthon

Illogical or umpolung reagent

Synthesis



(b) *Retrosynthetic analysis*



TM (126)

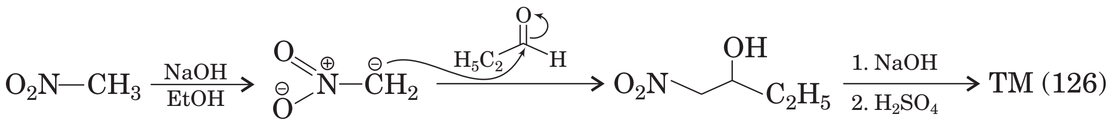
Illogical synthon

|||

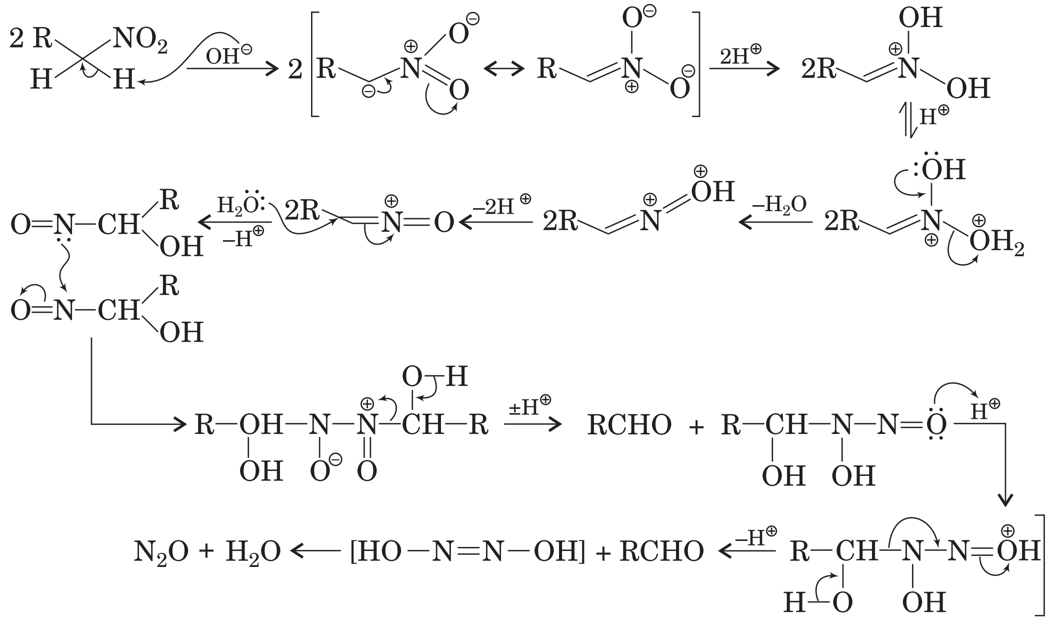
$\overset{\ominus}{C}H_2$—NO_2

Illogical reagent or synthetic equivalent

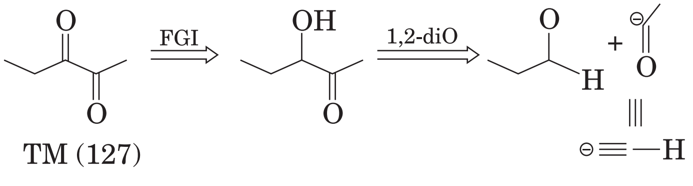
Synthesis



[When the conjugate bases (nitronate salts) of primary or secondary aliphatic nitro compounds are treated with sulphuric acid, they are converted to the corresponding carbonyl compounds. The reaction is called the *Nef reaction*. The mechanism of the reaction may be outlined as follows:

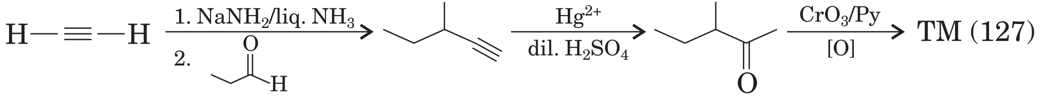


(c) *Retrosynthetic analysis*

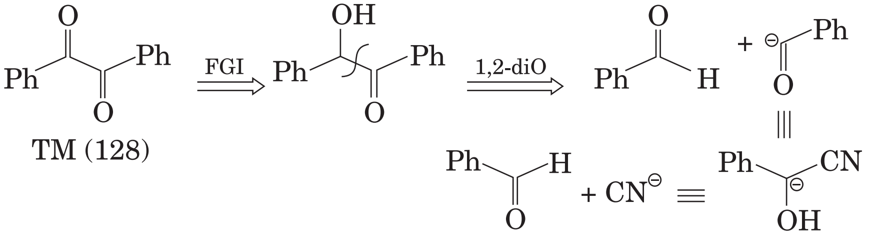


TM (127)

Synthesis

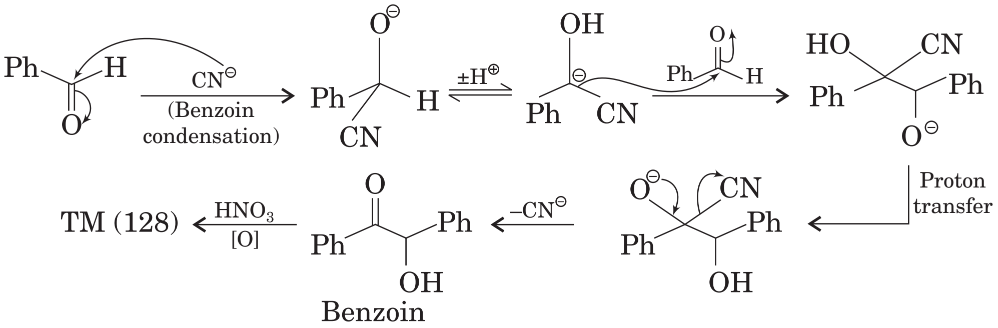


(d) *Retrosynthetic analysis*

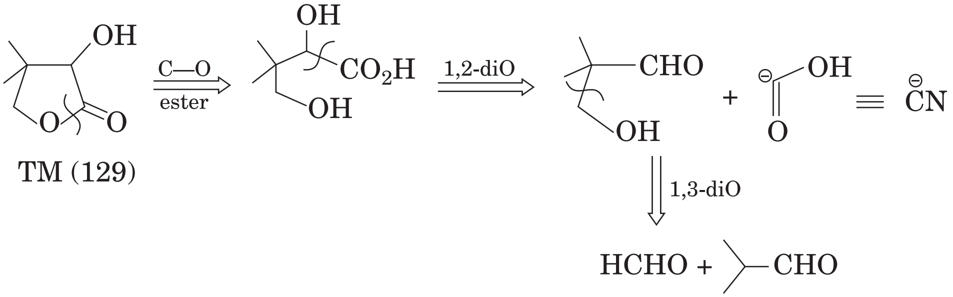


Cyanide ion transforms one molecule of benzaldehyde into an acyl anion. The synthesis of this target molecule is, therefore, carried out by benzoin condensation followed by oxidation.

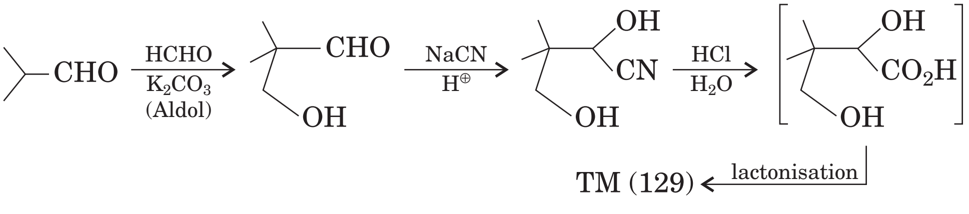
Synthesis



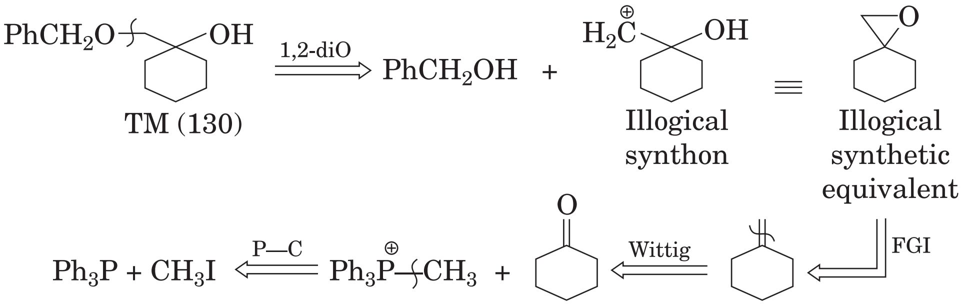
(e) *Retrosynthetic analysis*



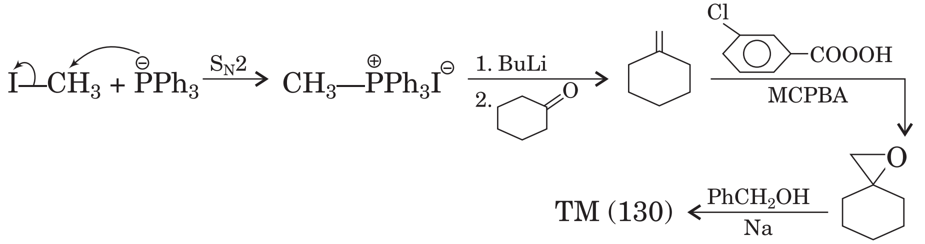
Synthesis



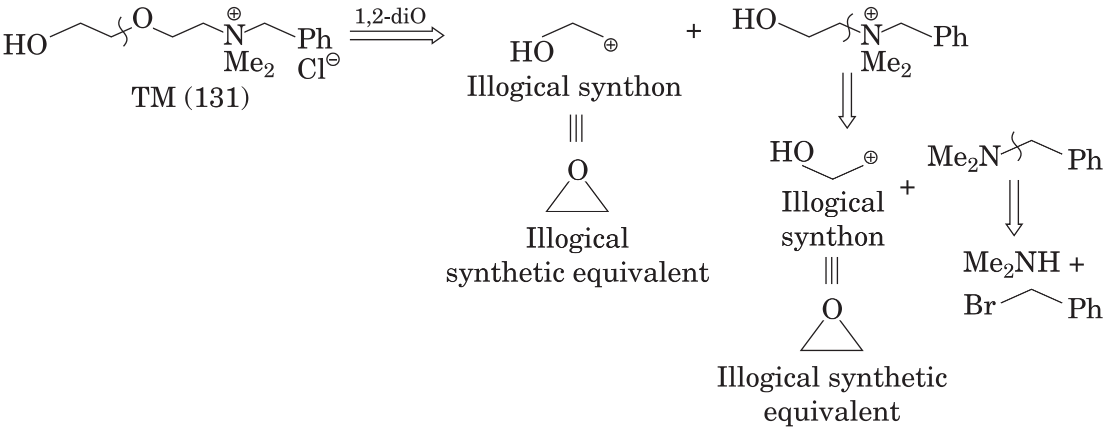
(f) *Retrosynthetic analysis*



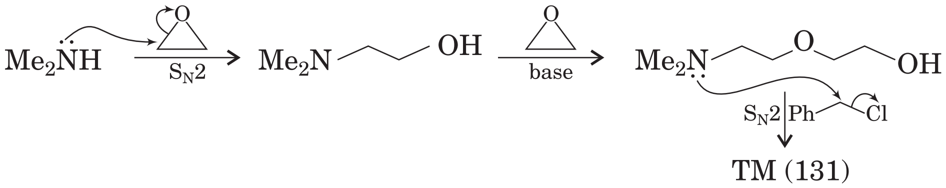
Synthesis



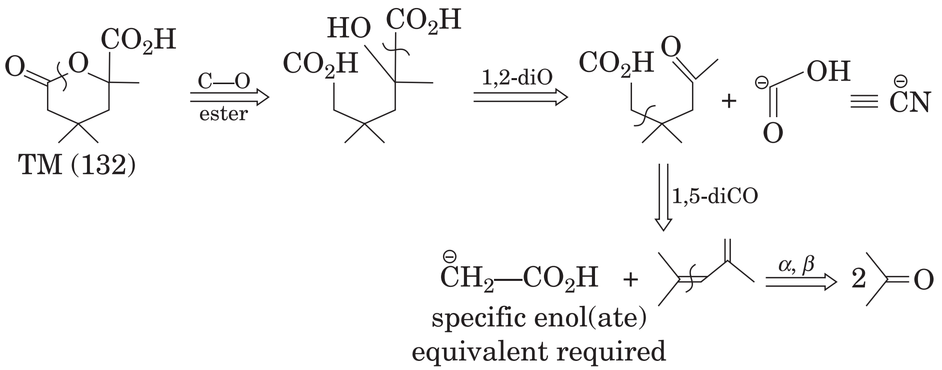
(g) *Retrosynthetic analysis*


TM (131)
1,2-diO
Illogical synthon
Illogical synthetic equivalent
Illogical synthon
Illogical synthetic equivalent
Me₂NH +
Br
Ph

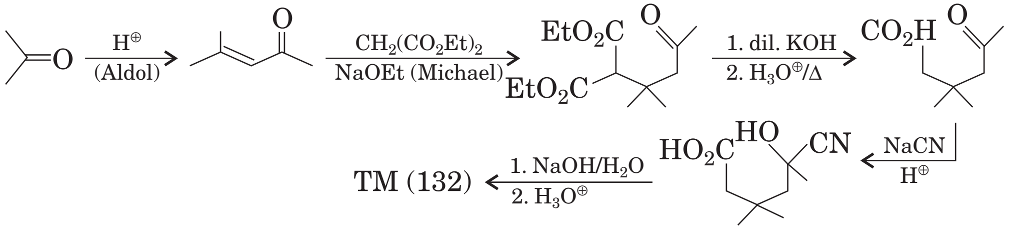
Synthesis



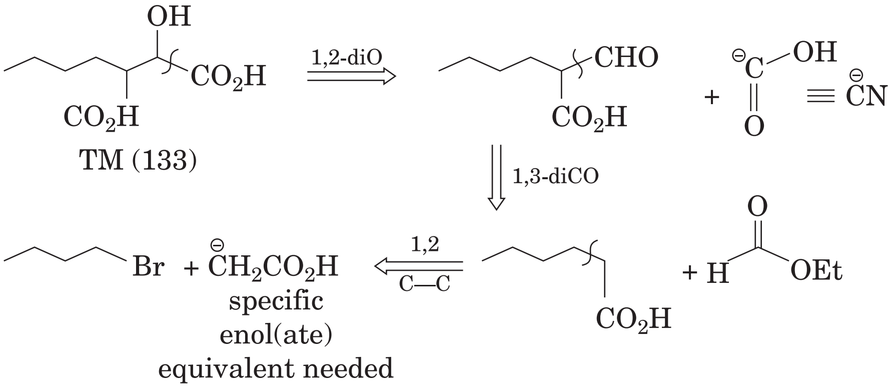
(h) *Retrosynthetic analysis*



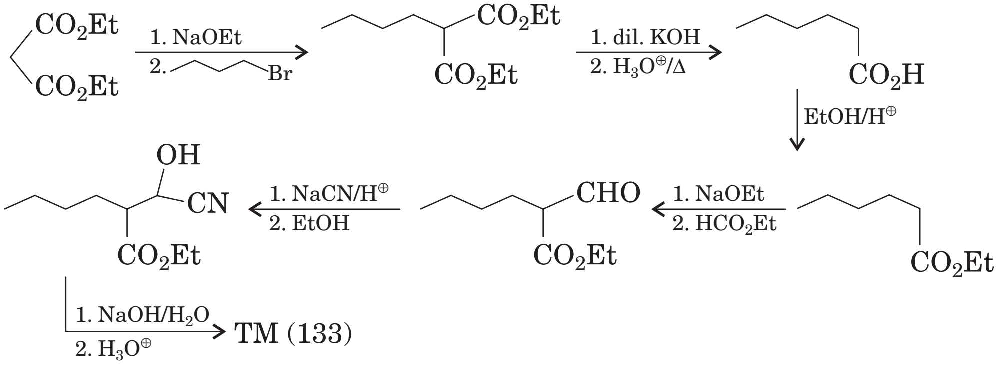
Synthesis


H⊕ (Aldol)
$CH_2(CO_2Et)_2$ NaOEt (Michael)
1. dil. KOH 2. $H_3O^{\oplus}/\Delta$
NaCN H⊕
1. NaOH/H_2O 2. $H_3O^{\oplus}$
TM (132)

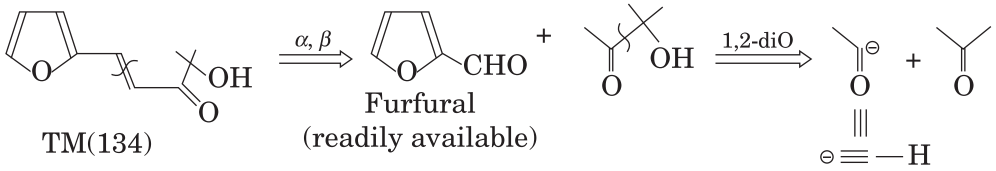
(i) *Retrosynthetic analysis*



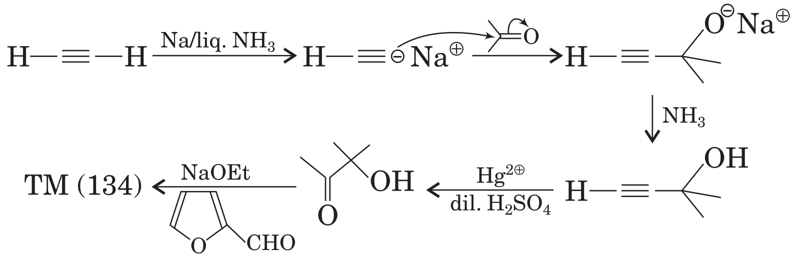
Synthesis


1. NaOEt 2. Br
1. dil. KOH 2. $H_3O^{\oplus}/\Delta$
EtOH/H⊕
1. NaOEt 2. HCO_2Et
1. NaCN/H⊕ 2. EtOH
1. NaOH/H_2O 2. $H_3O^{\oplus}$
TM (133)

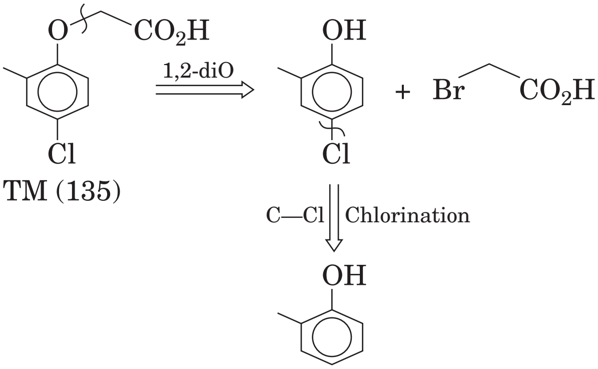
(j) *Retrosynthetic analysis*



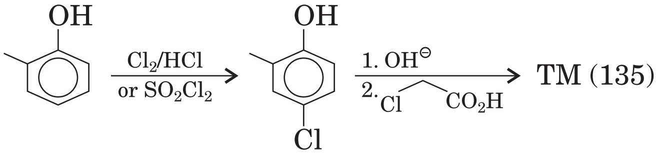
Synthesis



(h) *Retrosynthetic analysis*

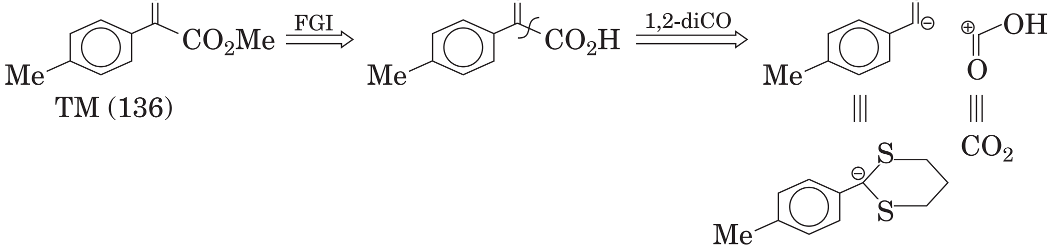


Synthesis

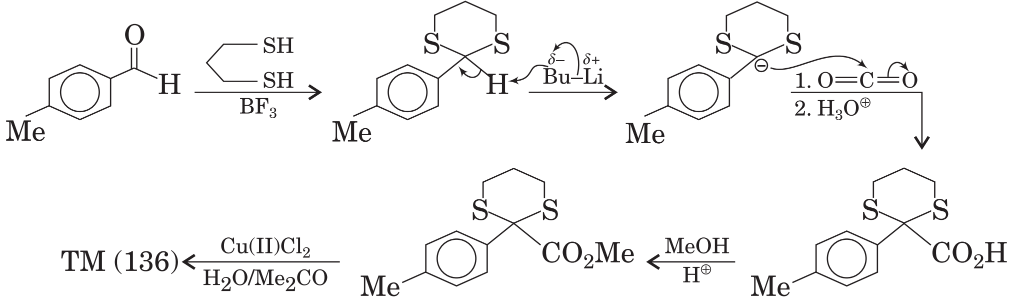


Chloroacetic acid is to be used because it is cheaper than bromoacetic acid.

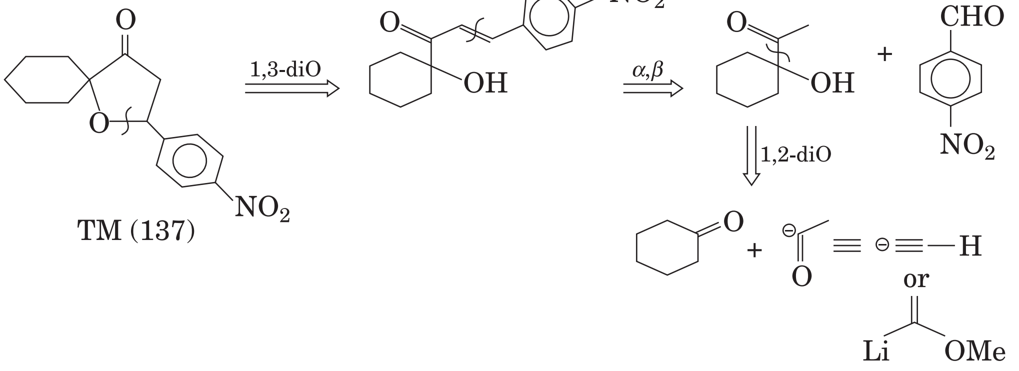
(l) *Retrosynthetic analysis*



Synthesis

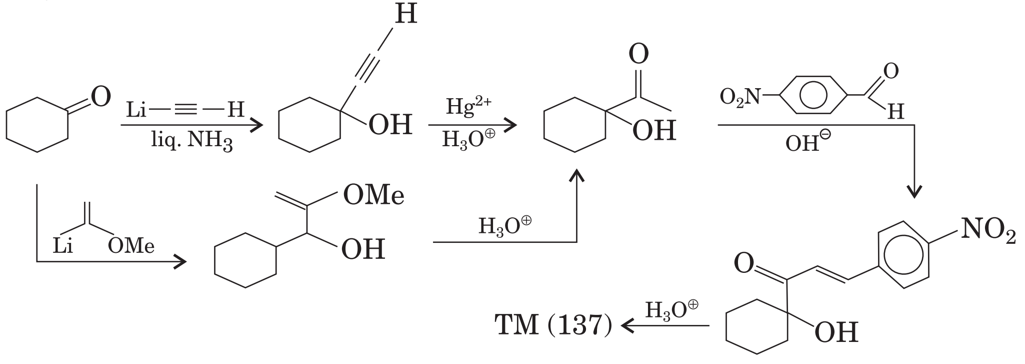


(m) *Retrosynthetic analysis*

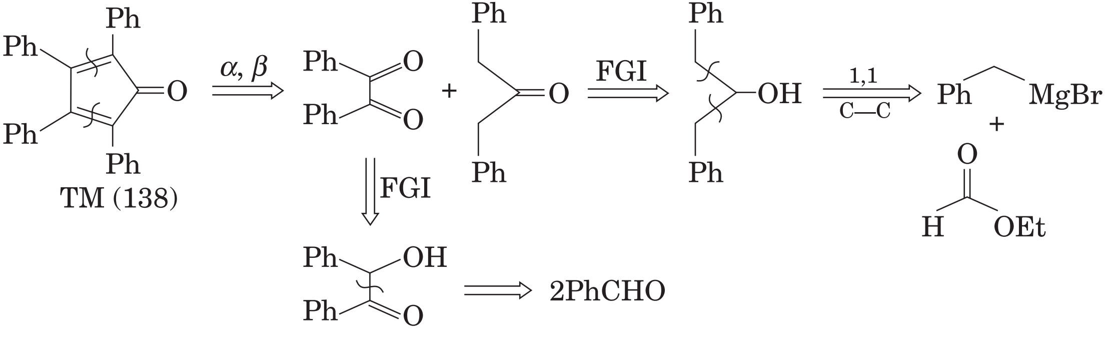


TM (137)

Synthesis

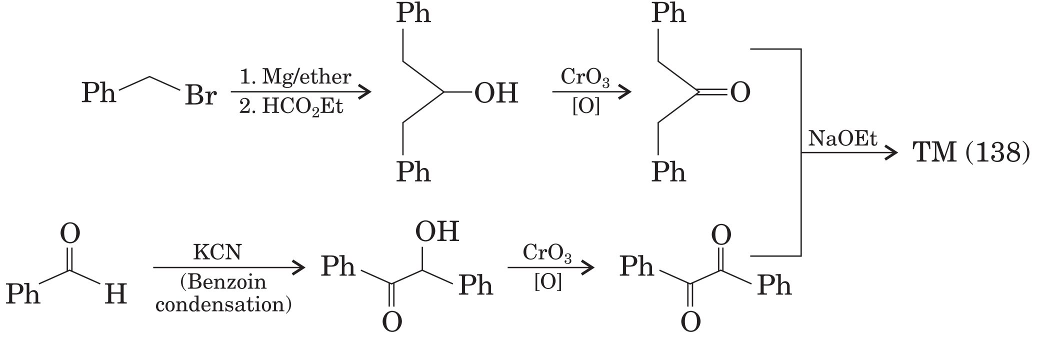


(n) *Retrosynthetic analysis*

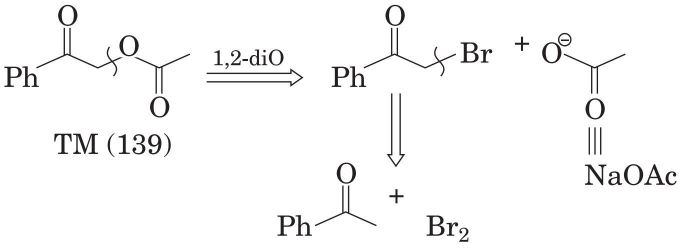


TM (138)

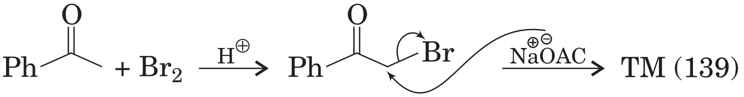
Synthesis



(o) *Retrosynthetic analysis*

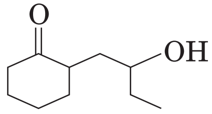


Synthesis



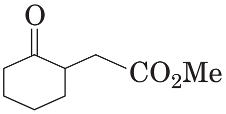
19. Give the forward synthesis of the following compounds (1,4-dioxygen systems) with proper retrosynthetic analysis involving illogical disconnections:

(a)



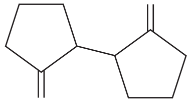
TM (140)

(b)



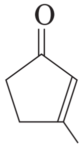
TM (141)

(c)



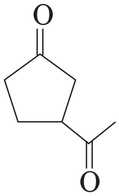
TM (142)

(d)



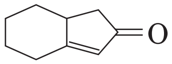
TM (143)

(e)



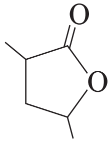
TM (144)

(f)



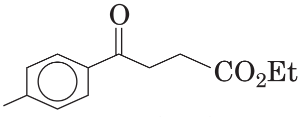
TM (145)

(g)



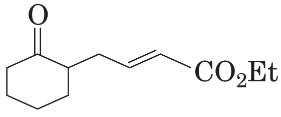
TM (146)

(h)



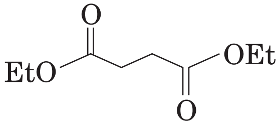
TM (147)

(i)



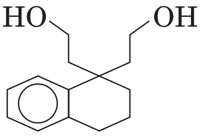
TM (148)

(j)



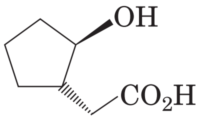
TM (149)

(k)



TM (150)

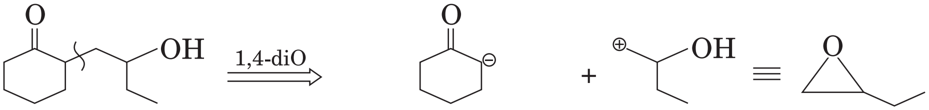
(l)



TM (151)

Solution

(a) *Retrosynthetic analysis*

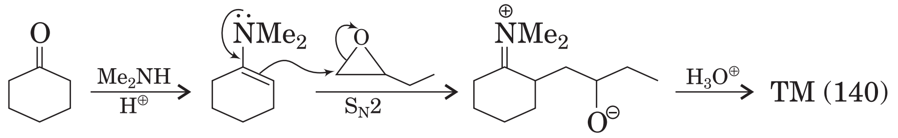


TM (140)

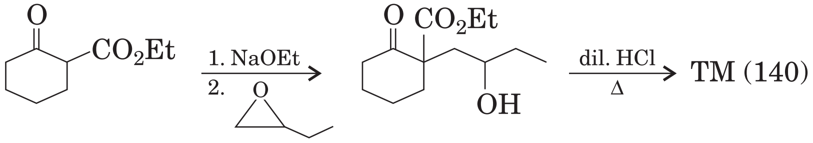
specific enol(ate) equivalent needed

Synthesis

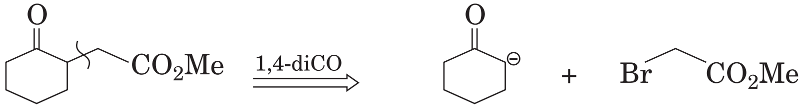
(i)



(ii) A –CO_2Et activating group may also be used to get the specific enol(ate) equivalent.



(b) *Retrosynthetic analysis*

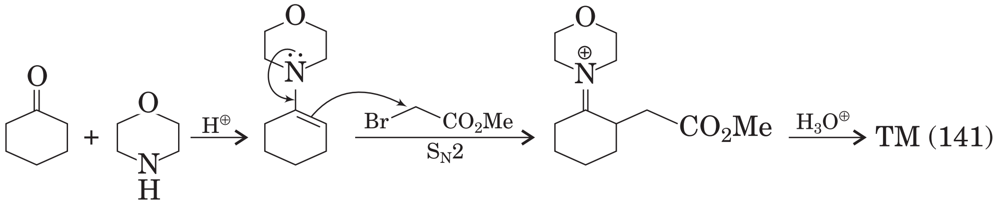


TM (141)

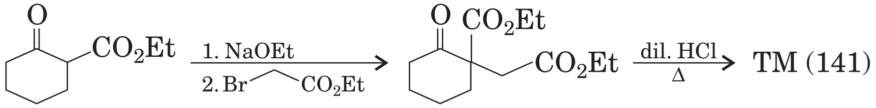
specific enol(ate) equivalent needed)

Synthesis

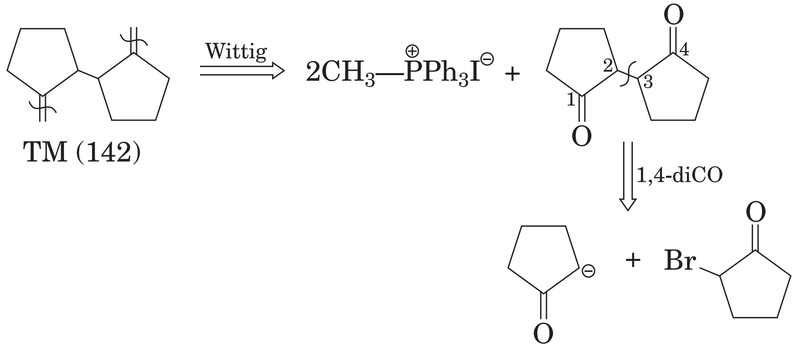
(i)



(ii)



(c) *Retrosynthetic analysis*

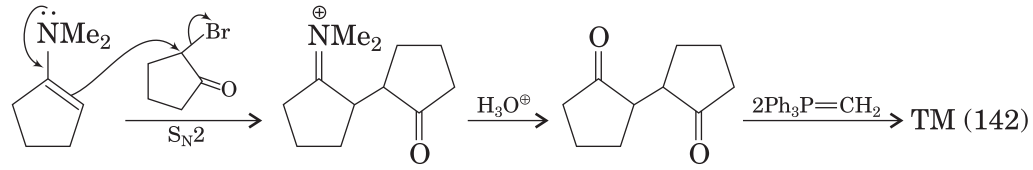


TM (142)

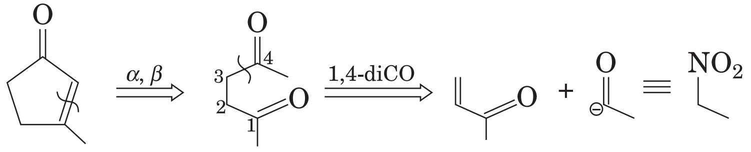
specific enol(ate)
equivalent needed

The diene (142) is actually a Wittig product which, in fact, is the only easy way to obtain the exocyclic double bonds. Wittig disconnection leads to a symmetrical 1,4-diketone. The bond between the ring is to be disconnected preferably.

Synthesis



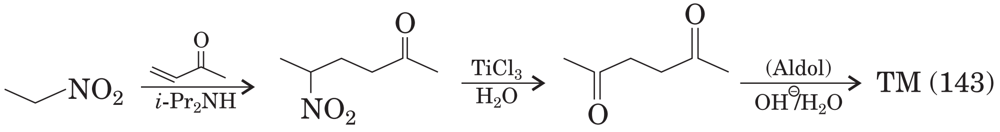
(d) *Retrosynthetic analysis*



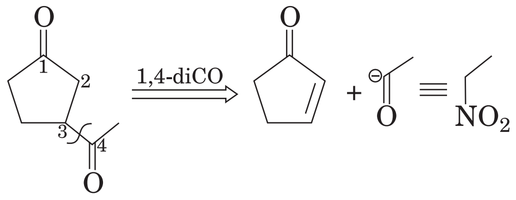
TM (143)

Nitro alkane anions added to enone in Michael fashion and therefore, behave as acyl anion equivalents in the synthesis of 1,4-diketones. This 1,4-disconnection is a preferable one because this leads to the readily available enone $CH_2{=}CHCOCH_3$.

Synthesis

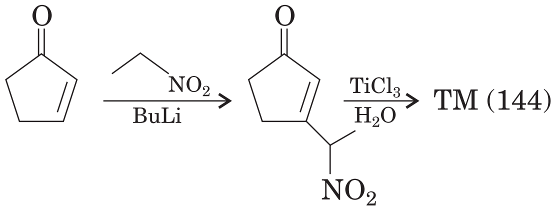


(e) *Retrosynthetic analysis*

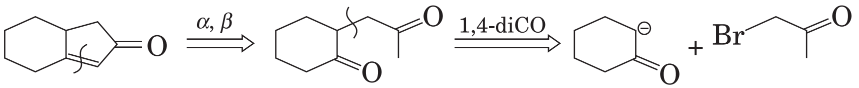


TM (144)

Synthesis



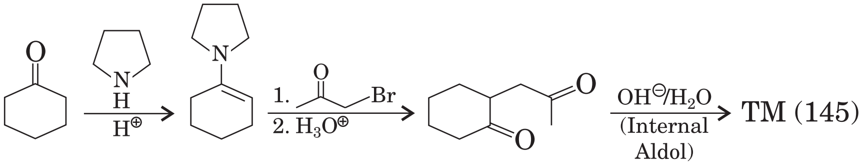
(f) *Retrosynthetic analysis (I)*



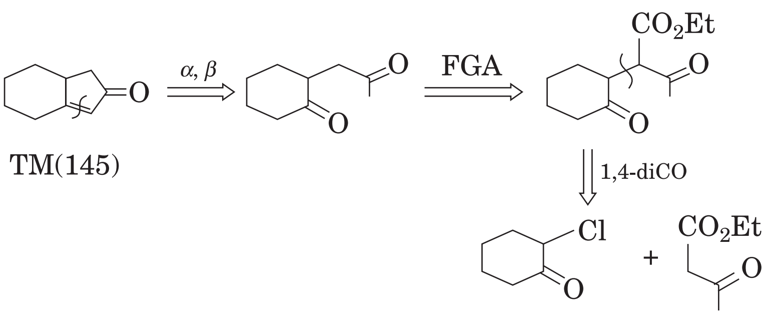
TM (145)

specific enol(ate)
equivalent needed

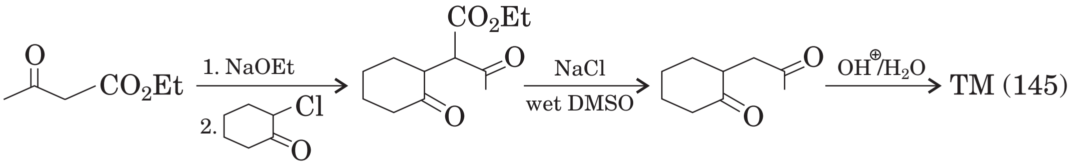
Synthesis (I)



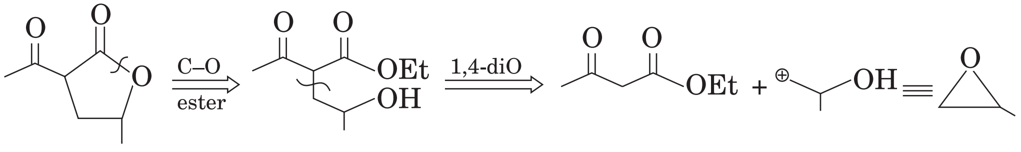
Retrosynthetic analysis (II)



Synthesis (II)

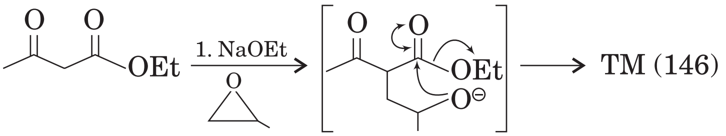


(g) *Retrosynthetic analysis*

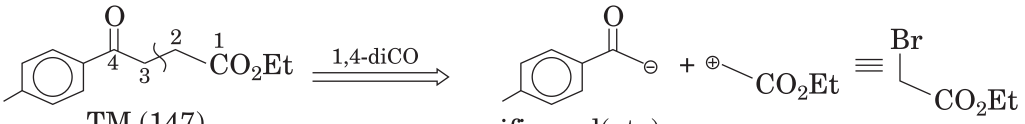


TM (146)

Synthesis



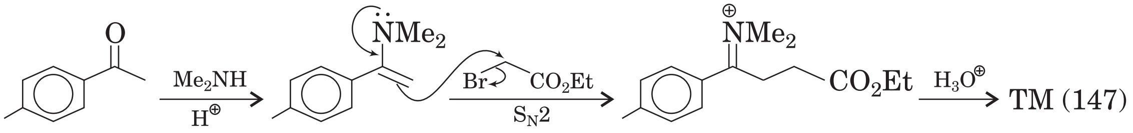
(h) *Retrosynthetic analysis*



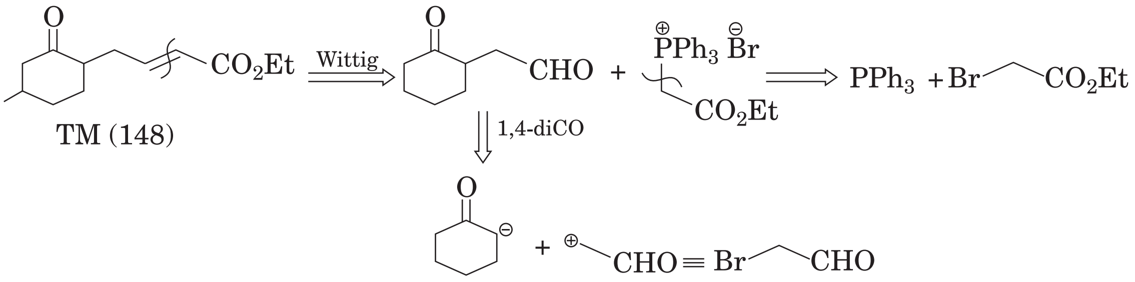
TM (147)

specific enol(ate)
equivalent needed

Synthesis

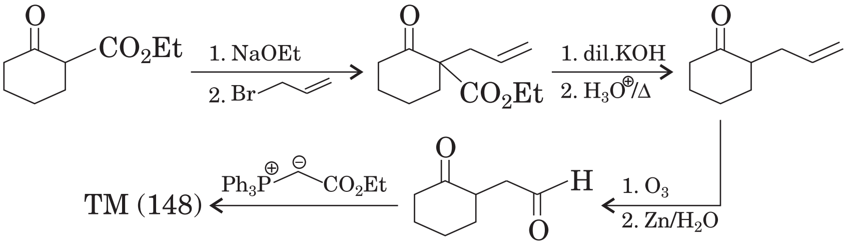


(i) *Retrosynthetic analysis*

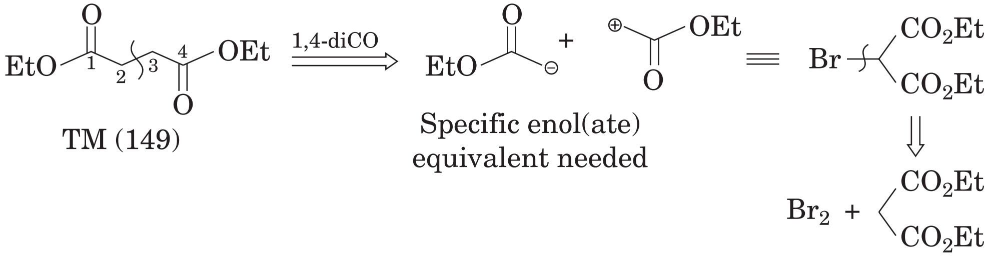


Since a 2-haloaldehyde is unstable (light sensitive), an allyl halide is used and the alkene is then subjected to ozonolysis with reductive work-up. As a result, a —CHO group is generated.

Synthesis

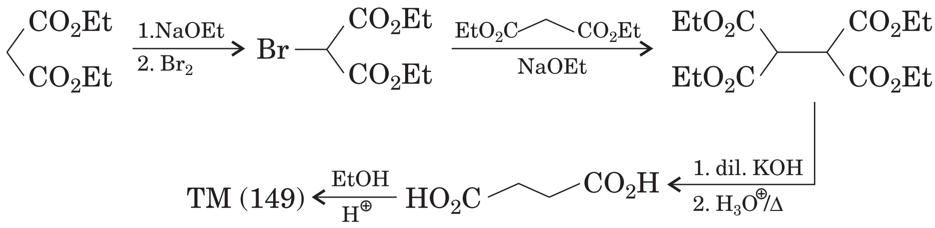


(j) *Retrosynthetic analysis*

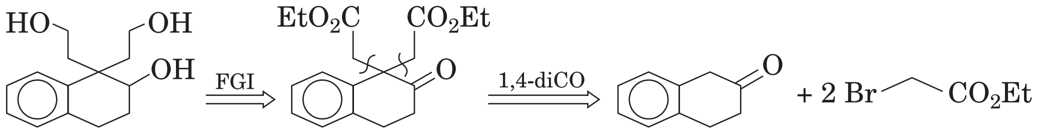


The specific enol(ate) equivalent is best represented by malonate. Therefore, the common starting material for both the synthons is diethyl malonate (DEM).

Synthesis

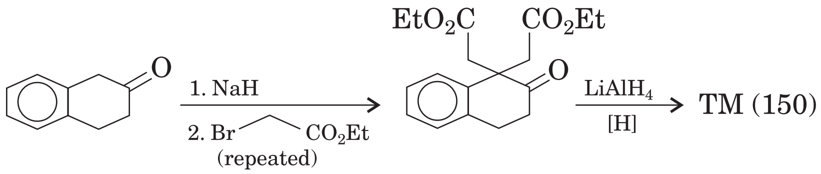


(k) *Retrosynthetic analysis*



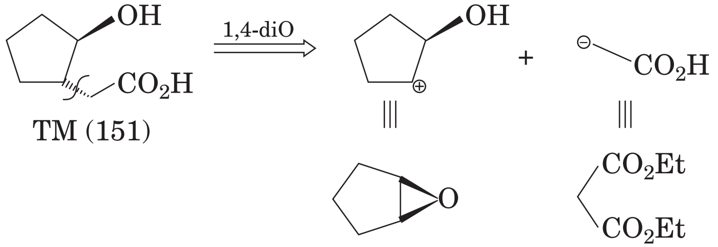
TM (150)

Synthesis



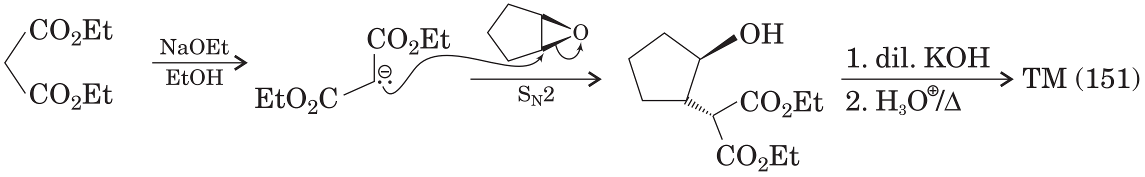
Because of conjugation with the benzene ring, the ketone enolises on the required side. In the first step, both alkylations occur readily.

(l) *Retrosynthetic analysis*



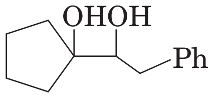
TM (151)

Synthesis



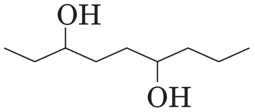
20. Design the synthesis of the following 1,2- and 1,4-difunctionalised compounds avoiding illogical disconnections:

(a)



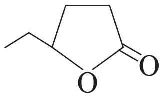
TM (152)

(b)



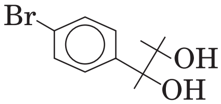
TM (153)

(c)



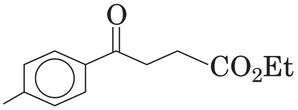
TM (154)

(d)



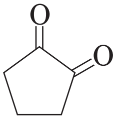
TM (155)

(e)



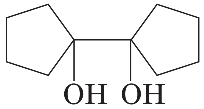
TM (156)

(f)



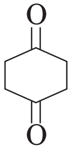
TM (157)

(g)



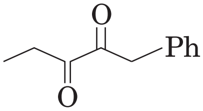
TM (158)

(h)



TM (159)

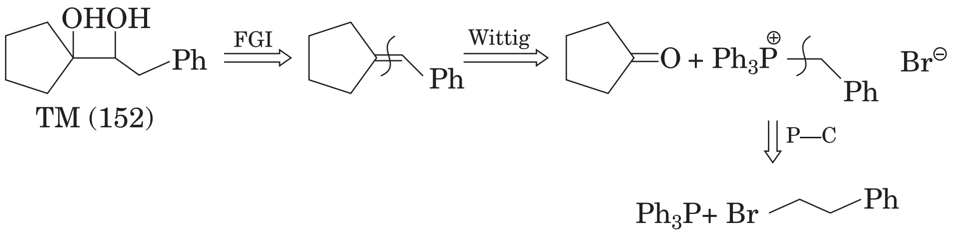
(i)



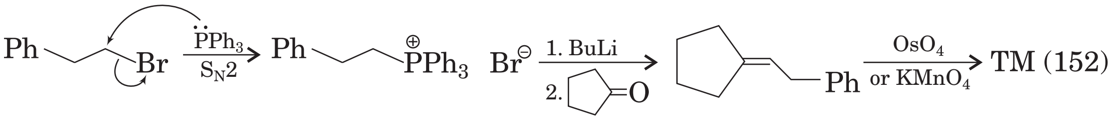
TM (160)

Solution

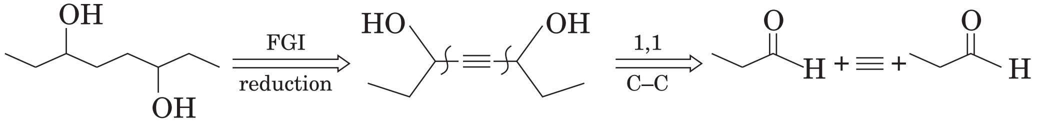
(a) *Retrosynthetic analysis*



Synthesis

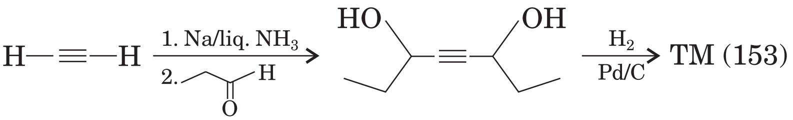


(b) *Retrosynthetic analysis*

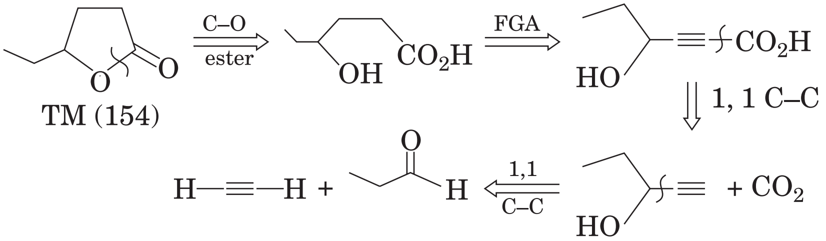


TM (153)

Synthesis

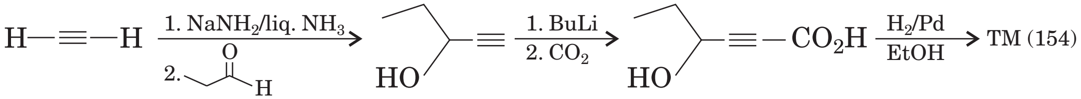


(c) *Retrosynthetic analysis*



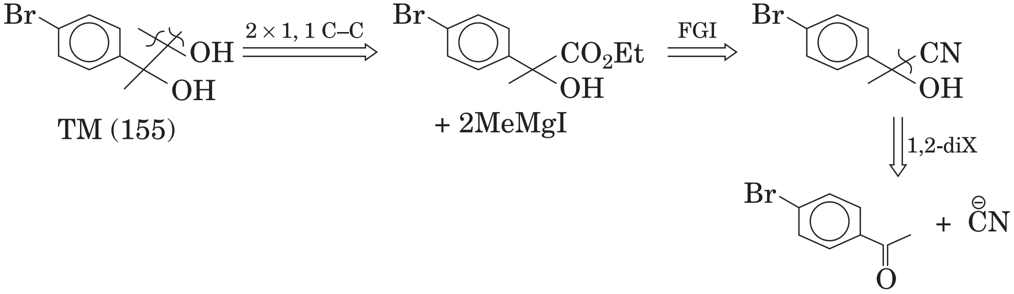
TM (154)

Synthesis



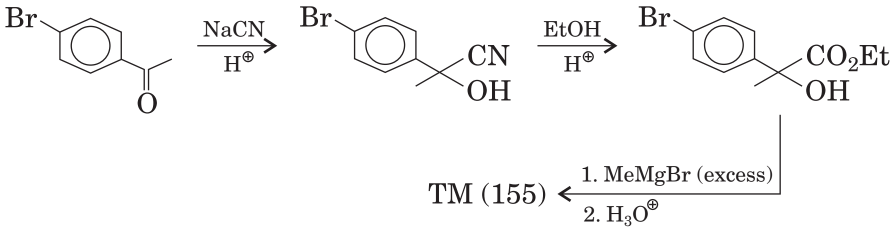
Cyclisation occurs spontaneously on hydrogenation because the groups come nearer to each other.

(d) *Retrosynthetic analysis*



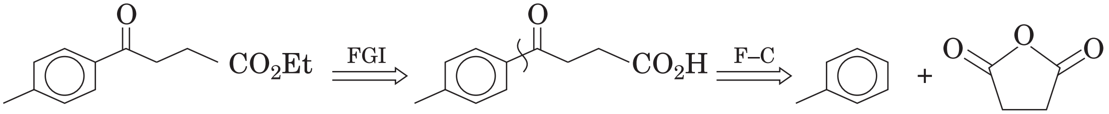
TM (155)

Synthesis



The nitrile is directly converted into the ester with acidic ethanol (hydrolysis followed by esterification) and an excess of Grignard reagent is required because the free —OH group destroys some of it (an acid–base reaction).

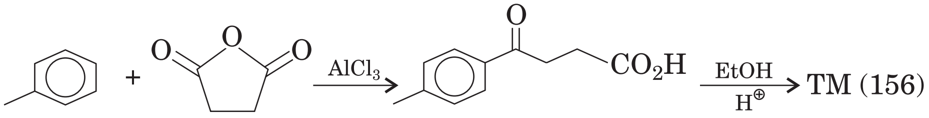
(e) *Retrosynthetic analysis*



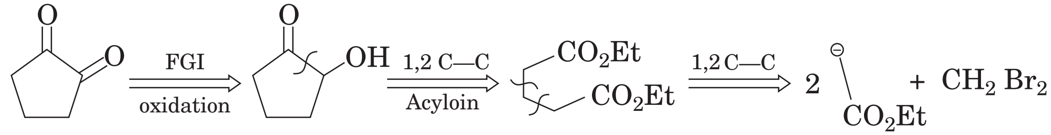
TM (156)

Umpolung can only be avoided by making the disconnection outside the relationship.

Synthesis



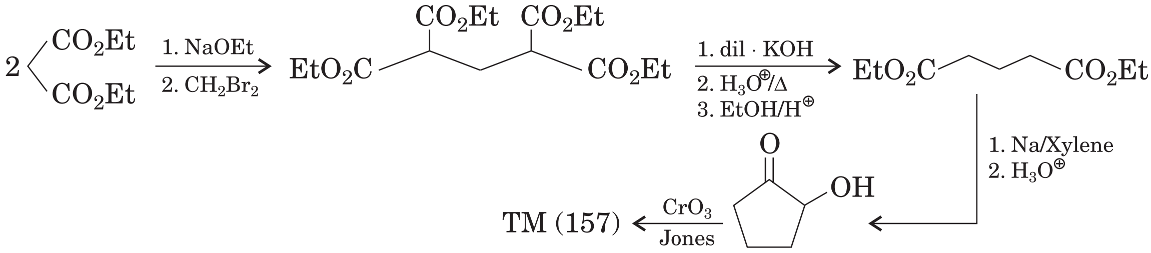
(f) *Retrosynthetic analysis*



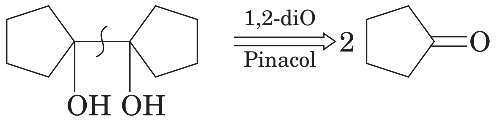
TM (157)

specific enol(ate) equivalent needed

Synthesis

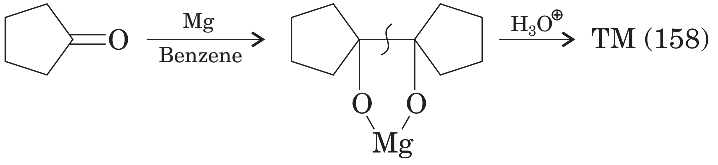


(g) *Retrosynthetic analysis*

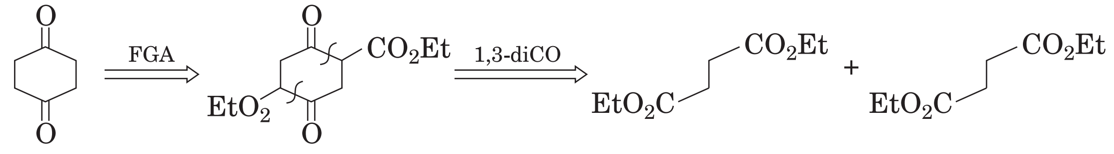


TM(158)

Synthesis

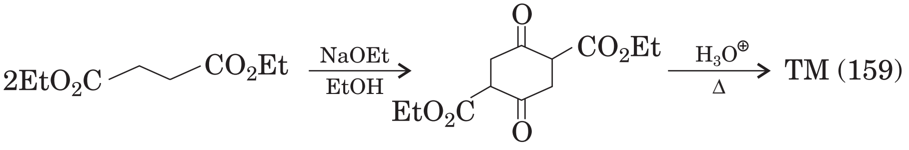


(h) *Retrosynthetic analysis*

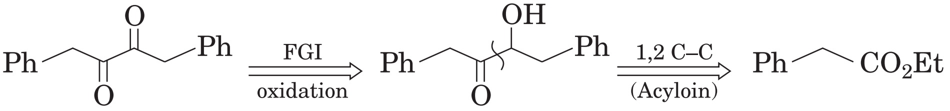


TM (159)

Synthesis

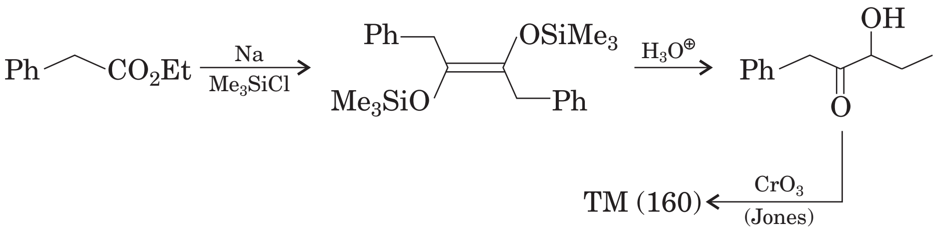


(i) *Retrosynthetic analysis*



TM (160)

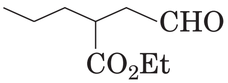
Synthesis



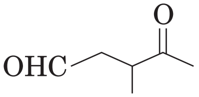
The acyloin reaction is carried out in the presence of Me_3SiCl which traps the intermediate dianion and removes the $EtO^{\ominus}$ byproduct. As a result, the side reactions are prevented.

21. How would you design the syntheses of the following target molecules (1,4-dicarbonyl compounds) using reconnection (an operation involving joining up a bond in the molecule which will be cleaved during synthesis)?

(a)

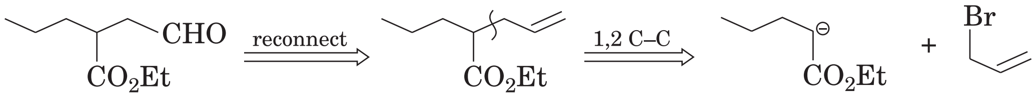


(b)



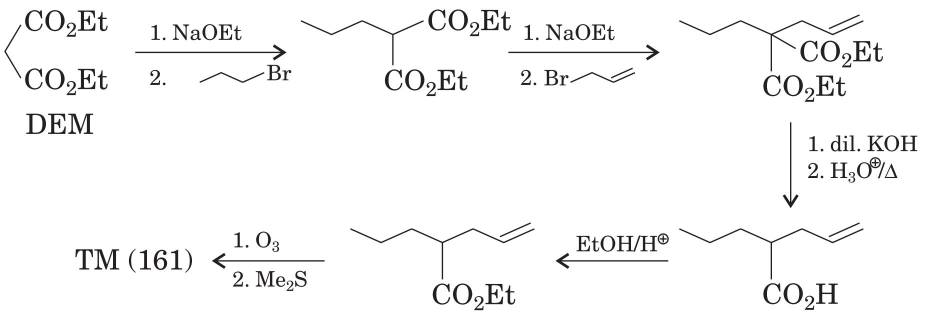
Solution

(a) *Retrosynthetic analysis*

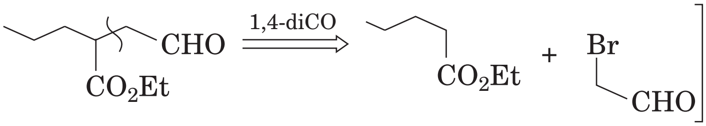


specific enol(ate)
equivalent needed

Synthesis

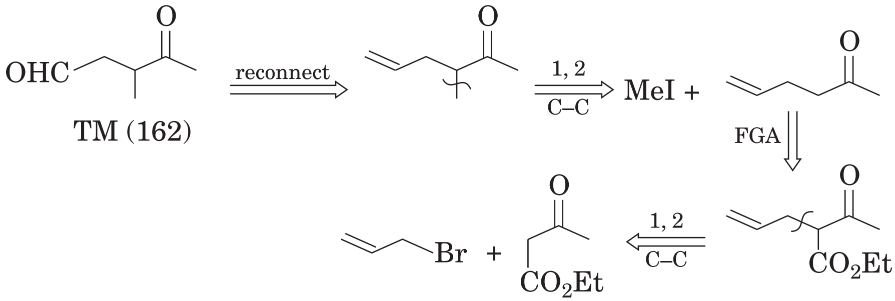


[It is to be noted that the following disconnection is not suitable because it leads to an α-halo aldehyde which, in fact, is highly reactive and very difficult to handle without protection. Reconnection can solve this problem.

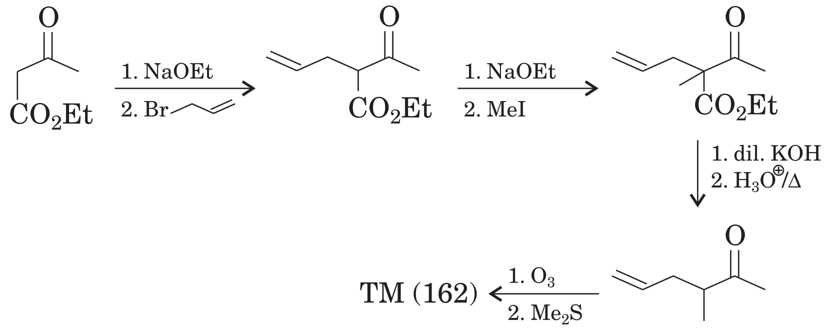


]

(b) *Retrosynthetic analysis*

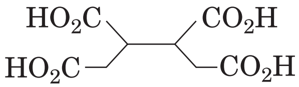


Synthesis



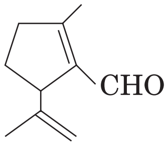
22. Following reconnection strategy how would you synthesize the target molecules given below:

(a)



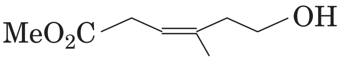
TM (163)

(b)



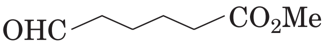
TM (164)

(c)



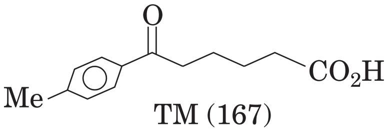
TM (165)

(d)



TM (166)

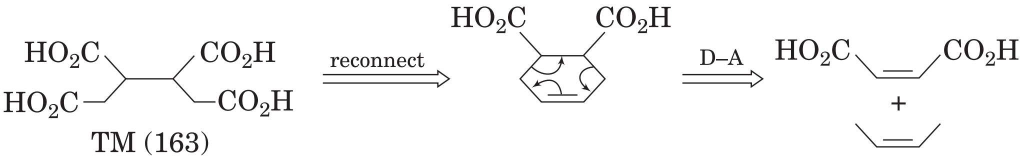
(e)



TM (167)

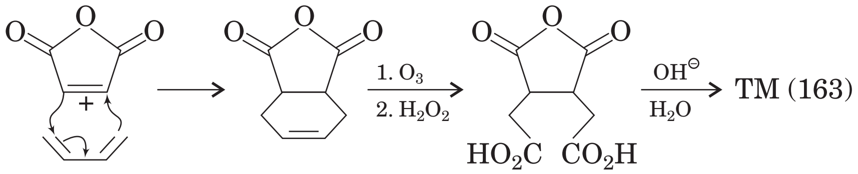
Solution

(a) *Retrosynthetic analysis*

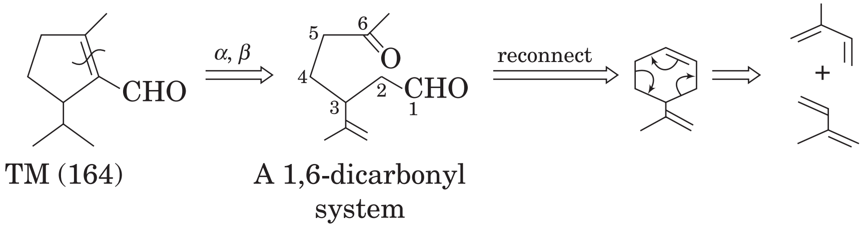


Synthesis

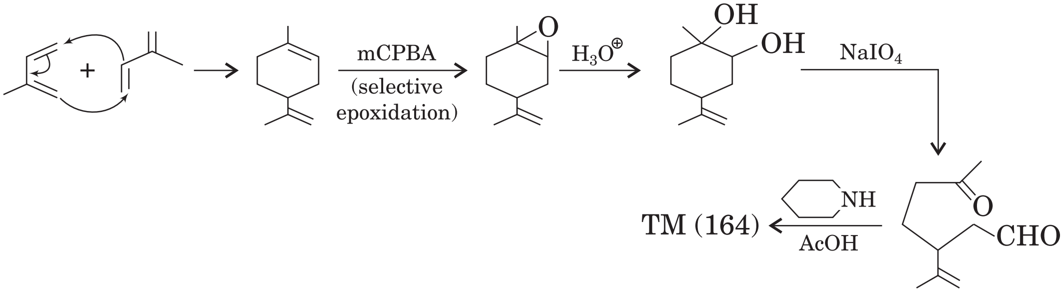
Maleic anhydride is the most appropriate reagent for this synthesis.



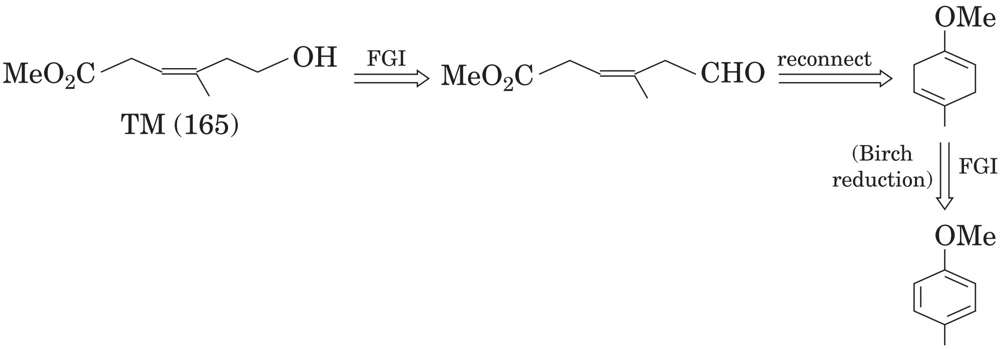
(b) *Retrosynthetic analysis*



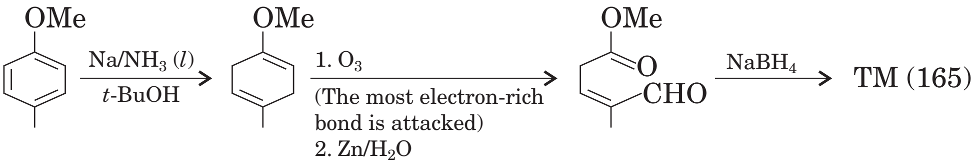
Synthesis



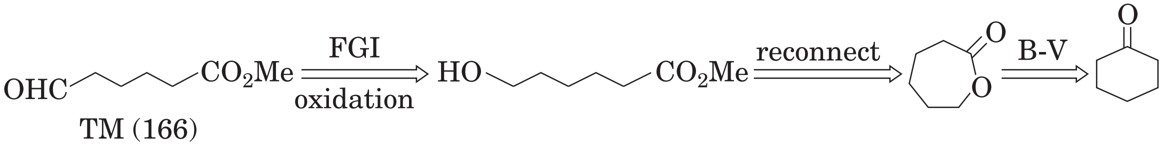
(c) *Retrosynthetic analysis*



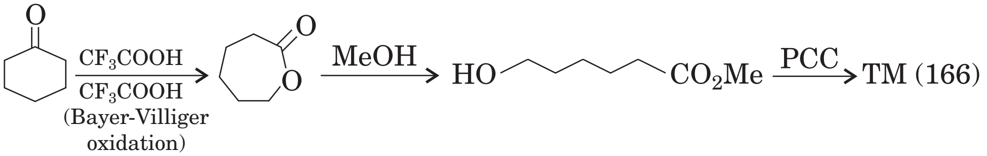
Synthesis



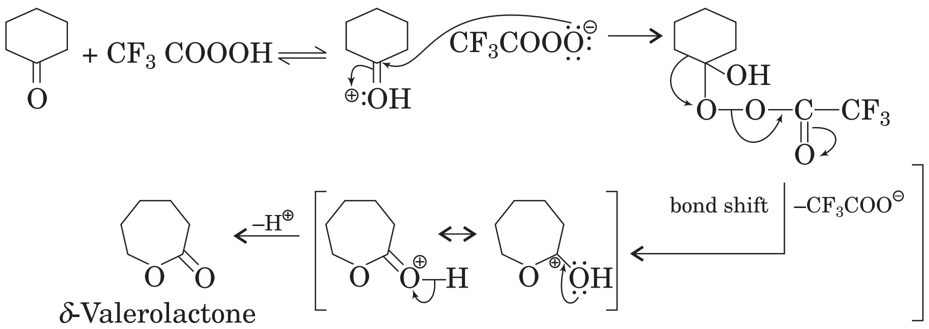
(d) *Retrosynthetic analysis*



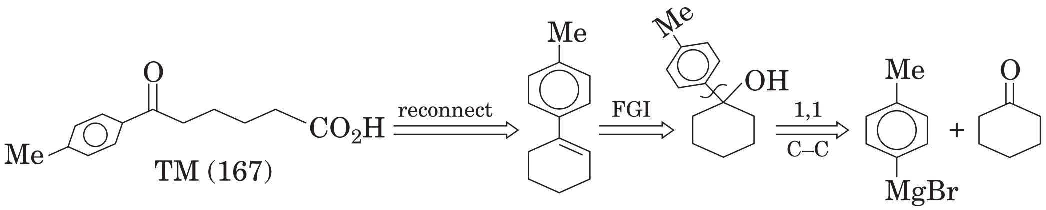
Synthesis



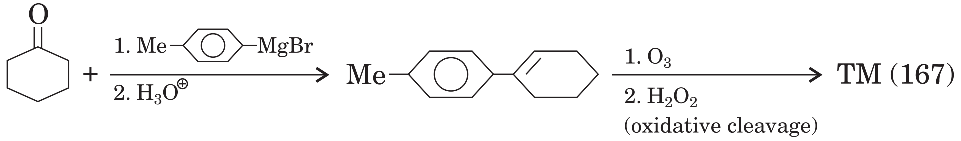
[*Mechanism*:



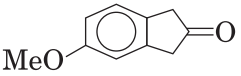
(e) *Retrosynthetic analysis*



Synthesis



23. Using disconnection approach, design two suitable syntheses for the following target molecule:

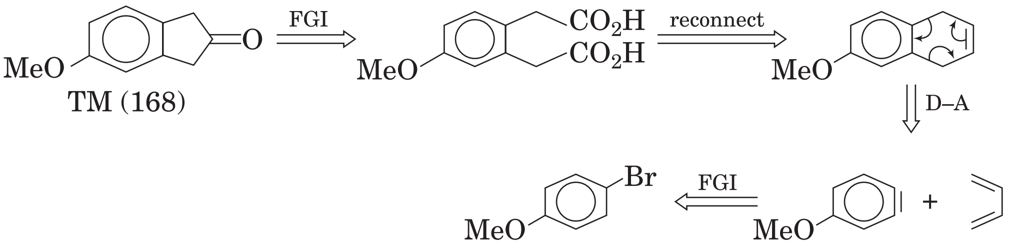


TM (168)

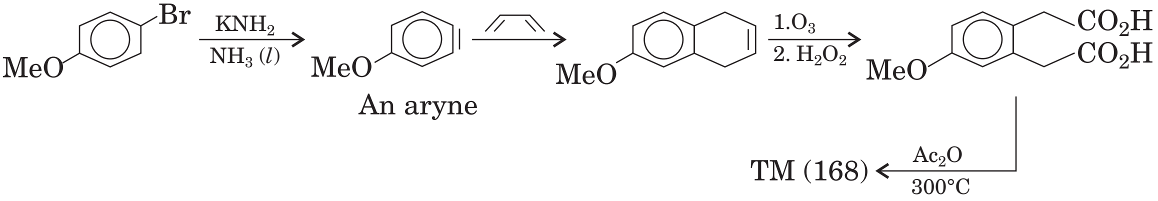
Solution

This target molecule may be synthesized in two ways, one of which involves reconnection strategy. These are as follows:

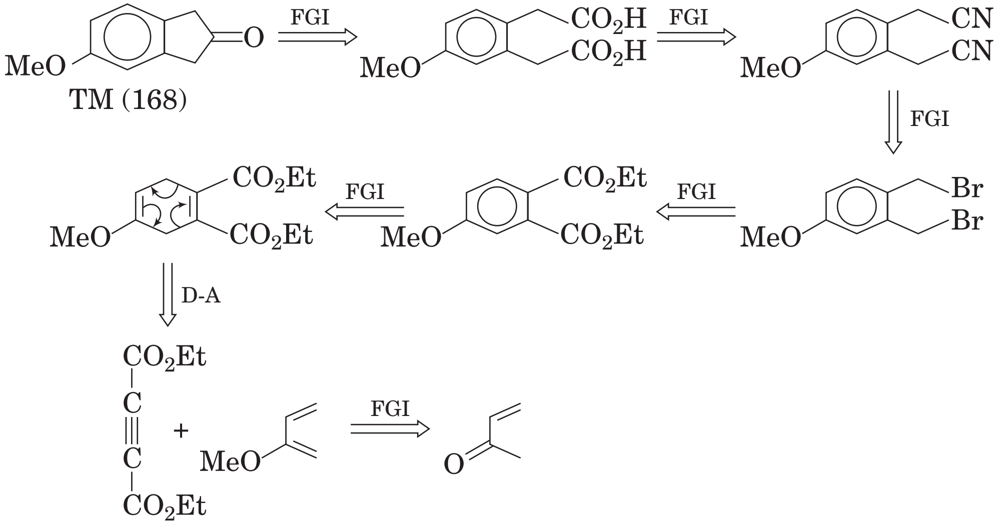
Retrosynthetic analysis (I)



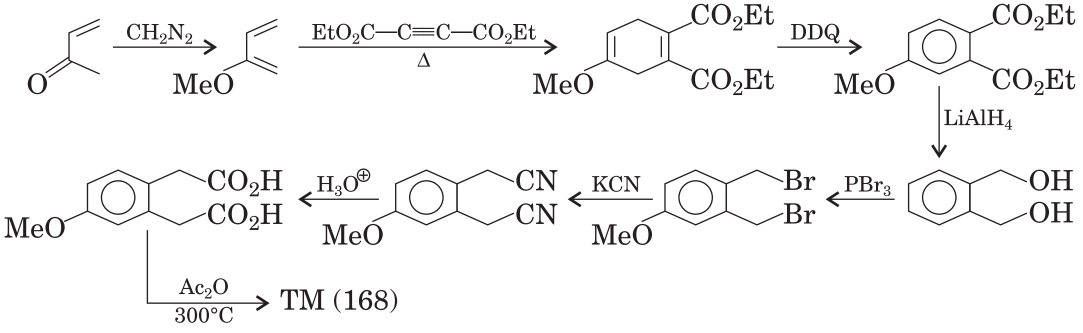
Synthesis (I)



Retrosynthetic analysis (II)

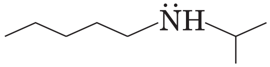


Synthesis (II)



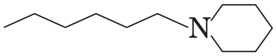
24. Outline the synthesis of each of the following target molecules (amines) with proper retrosynthetic analysis:

(a)



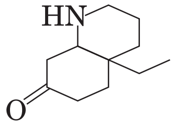
TM (169)

(b)



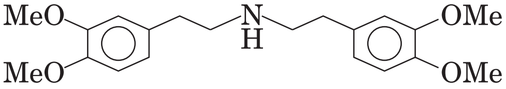
TM (170)

(c)



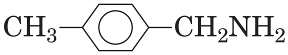
TM (171)

(d)



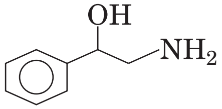
TM (172)

(e)



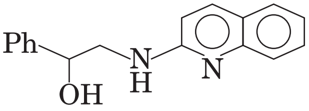
TM (173)

(f)



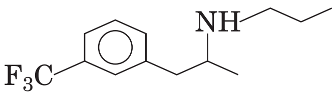
TM (174)

(g)



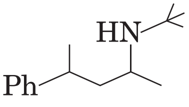
TM (175)

(h)



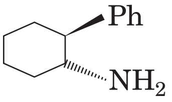
TM (176)

(i)



TM (177)

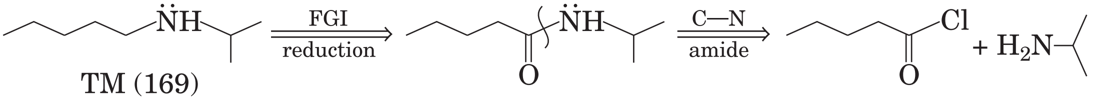
(j)



TM (178)

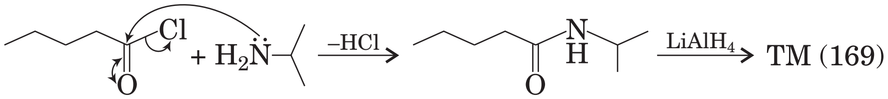
Solution

(a) *Retrosynthetic analysis (I)*

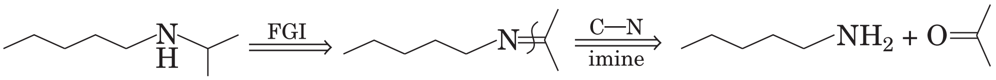


TM (169)

Synthesis (I)

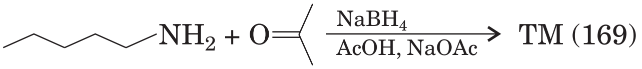


Retrosynthetic analysis (II)

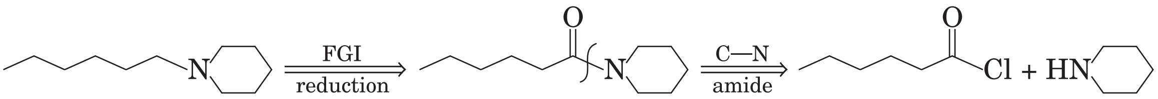


TM (169)

Synthesis (II)



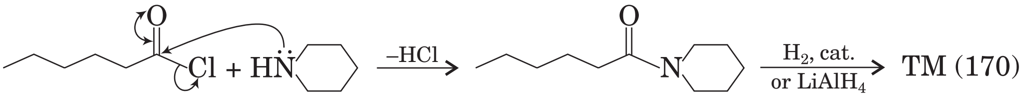
(b) *Retrosynthetic analysis*



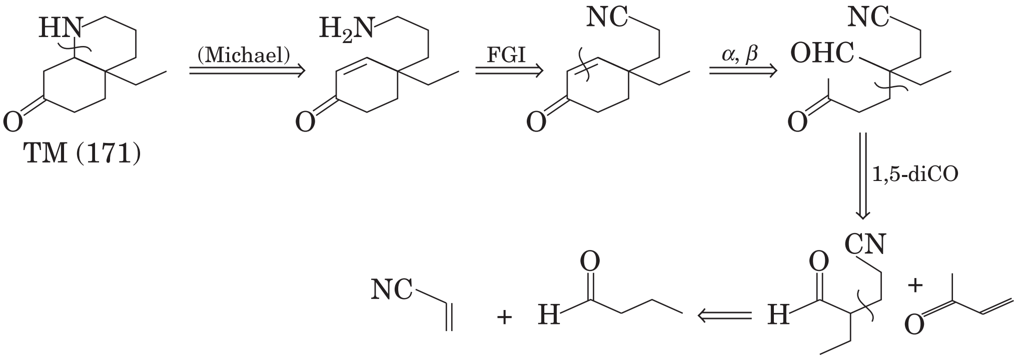
TM (170)

Because the cyclic amine piperidine is readily available, the exocyclic methylene group is chosen as the site for FGI.

Synthesis

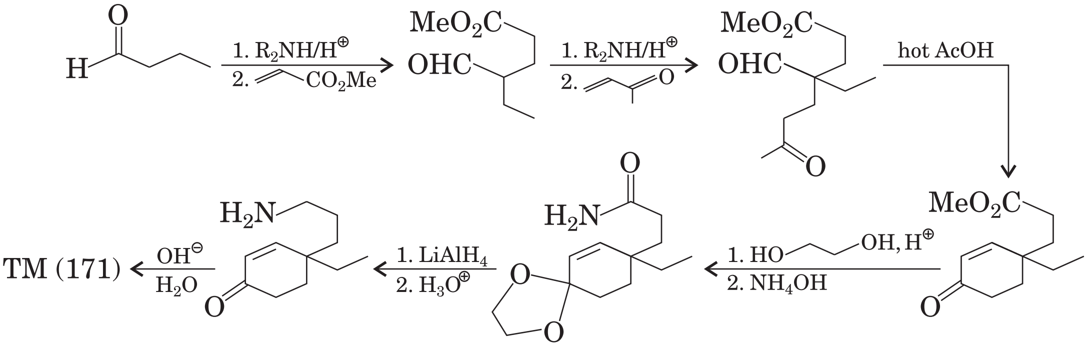


(c) *Retrosynthetic analysis*

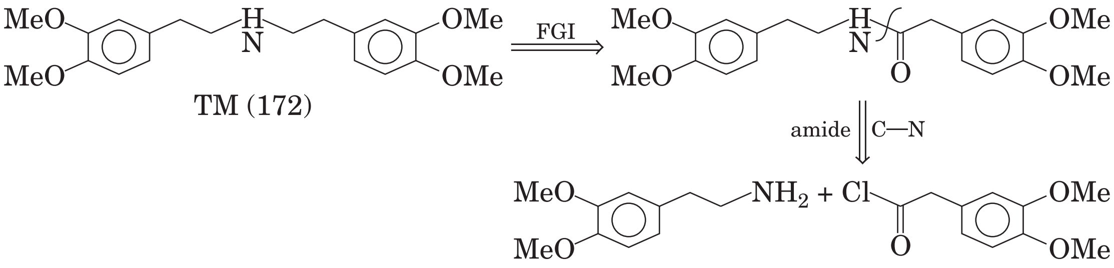


Synthesis

It is better to use methyl acrylate instead of acrylonitrile.

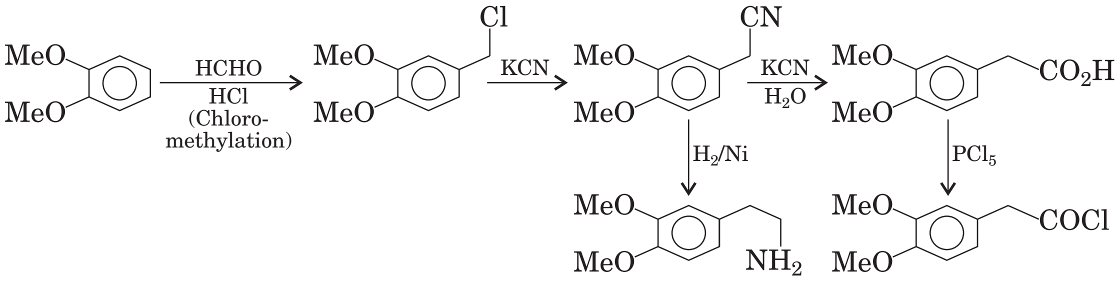


(d) *Retrosynthetic analysis*



Synthesis

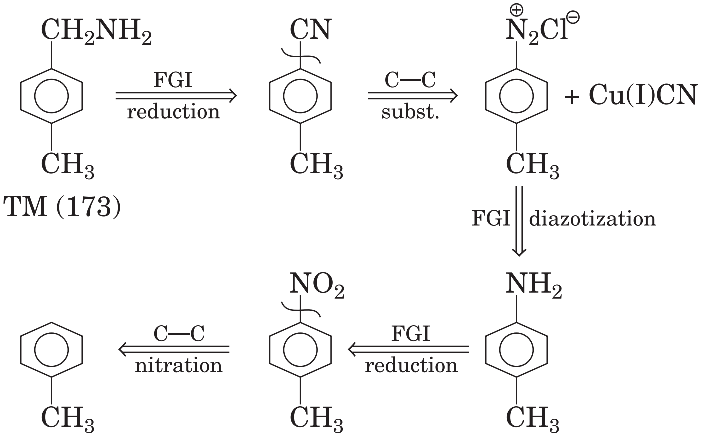
The most economical route to make both the acid chlorine and the amine is from the nitrile.



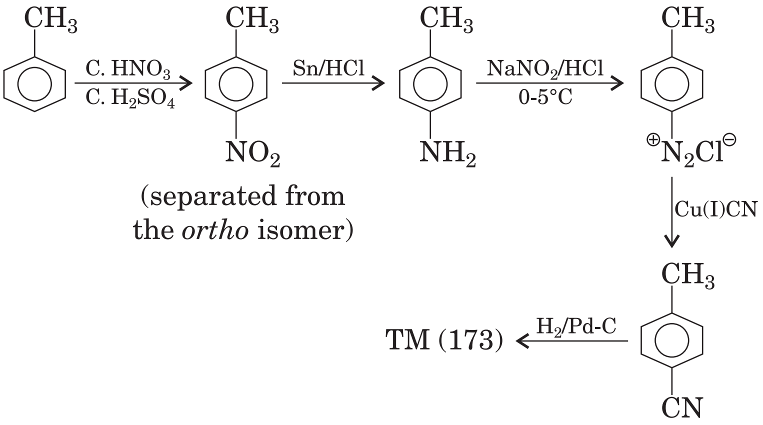
(A) (B)

Now, (A) + (B) $\longrightarrow$ TM (172)

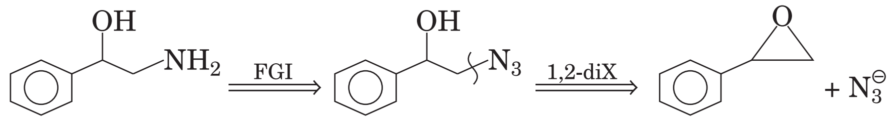
(e) *Retrosynthetic analysis*



Synthesis

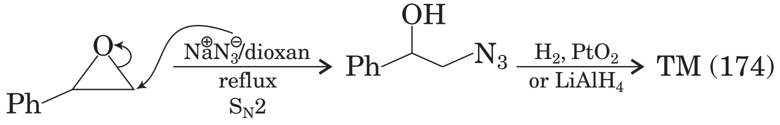


(f) *Retrosynthetic analysis*

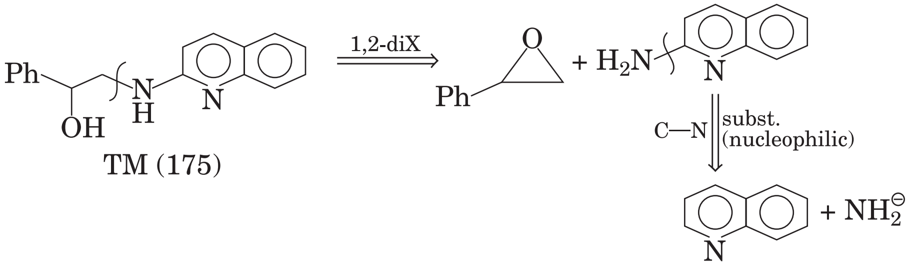


TM (174)

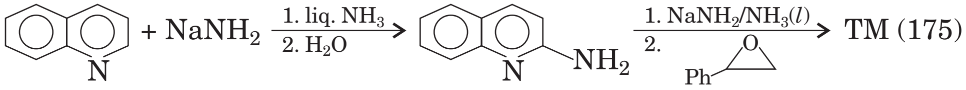
Synthesis



(g) *Retrosynthetic analysis*

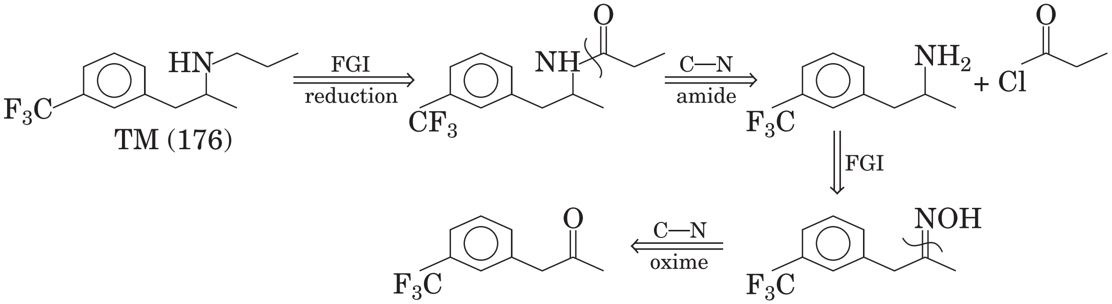


Synthesis

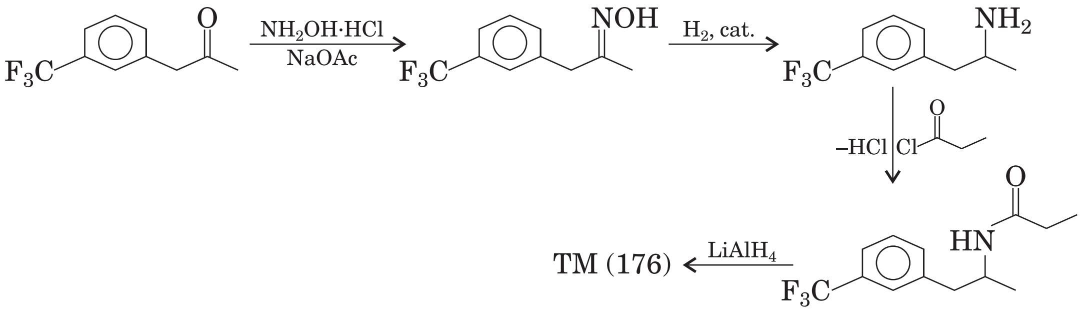


Isoquinoline

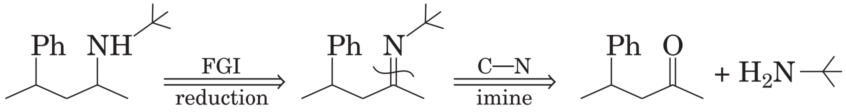
(h) *Retrosynthetic analysis*



Synthesis

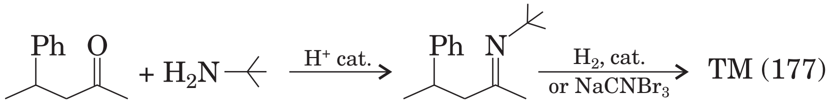


(i) *Retrosynthetic analysis*



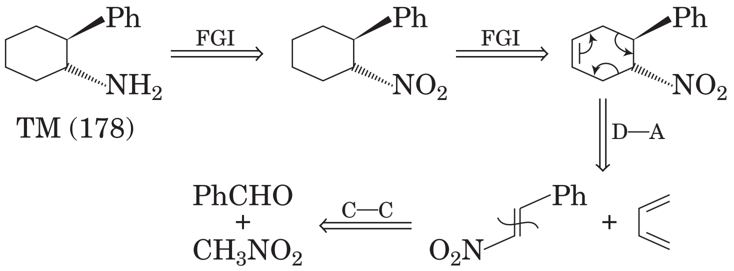
TM (177)

Synthesis



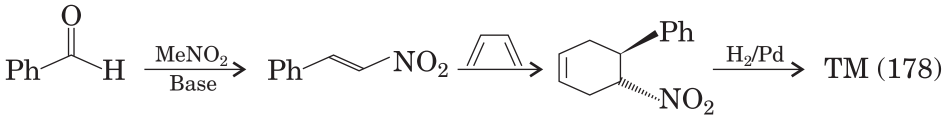
There is no CH_2 group next to nitrogen, and therefore, the imine route is chosen.

(j) *Retrosynthetic analysis*



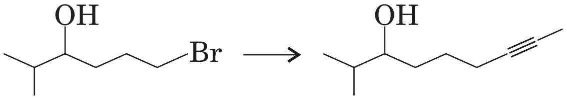
TM (178)

Synthesis

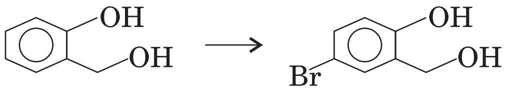


25. How would you carry out the following transformations?

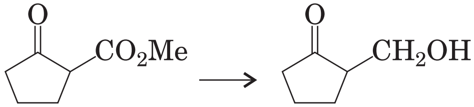
(a)



(b)

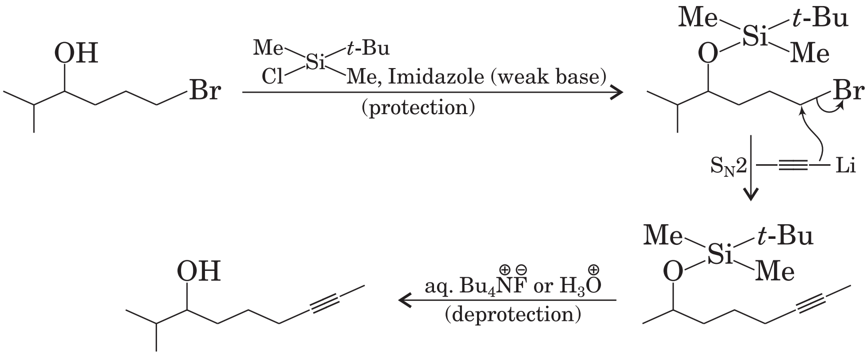


(c)

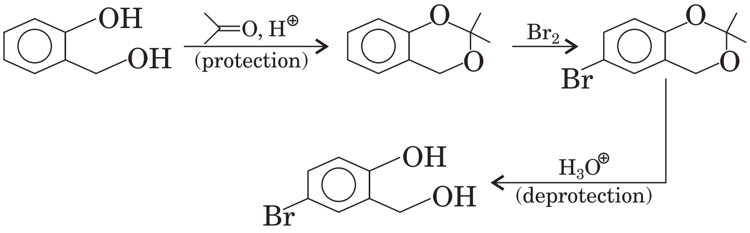


Solution

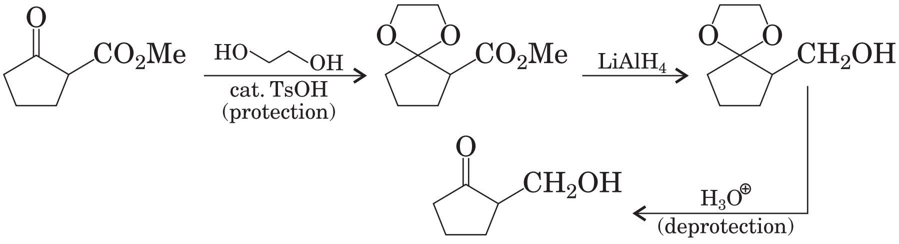
(a) Alkylation of the alkynyl anion with this bromo-alcohol is not possible because the anion being a strong base readily deprotonates the hydroxyl group. For this reason, the hydroxyl group is to be protected.



(b) Since the alcoholic —OH group in the starting compound is susceptible to oxidation by bromine, it is protected by forming an acetal.



(c) Since the $>$C=O group is much more readily reduced than the ester group, it is to be protected.

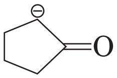


STUDY PROBLEMS

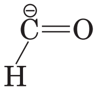
1. Write down the synthetic equivalents for the following synthones:

(a) $\overset{\ominus}{C}H_2COOH$ (b) $\overset{\oplus}{C}H_2CH_2OH$ (c) $CH_3{-}\overset{\oplus}{C}{=}O$

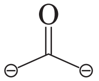
(d) $\overset{\oplus}{C}H_2CO_2Et$ (e) $\overset{\ominus}{C}H_2CH_2COCH_3$ (f)



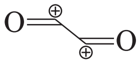
(g)



(h)



(i)



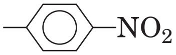
(j) $\overset{\ominus}{C}OOH$ (k) $\overset{\ominus}{C}H_2CO_2Et$ (l) $\overset{\ominus}{C}H_3$

(m) $\overset{\ominus}{\underset{\ominus}{C}}H_2$ (n) $Br^{\ominus}$ (o) $Me_2\overset{\oplus}{C}OH$

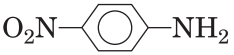
(p) $\overset{\ominus}{C}H_2CH_2CN$ (q) $Me{-}C{\equiv}C^{\oplus}$ (r) $\overset{\oplus}{N}H_2$

2. Which one of the groups in each of the following target molecules should be disconnected first and why?

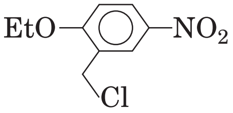
(a)



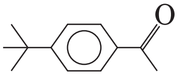
(b)



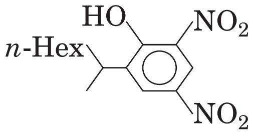
(c)



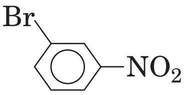
(d)



(e)

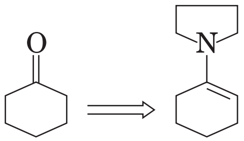


(f)

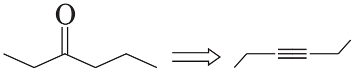


3. Make the following FGI's:

(a)

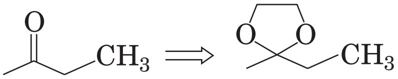


(b)



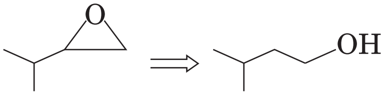
(c) —COOH ⇒ –CN

(d)

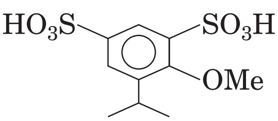


(e) —COOEt ⇒ —CH_2OH

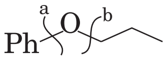
(f)



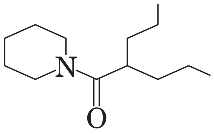
4. Write down the three strategies (differing in the order of events) for the synthesis of the following target molecule. Which one is expected to be the best one and why?

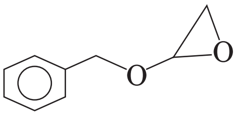


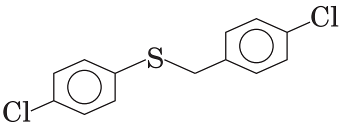
5. Which of the following two disconnections (a and b) you find to be a good choice and why?

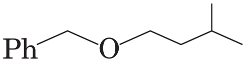


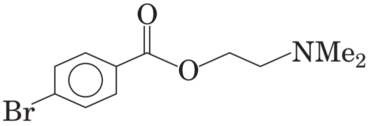
6. Using disconnection approach (one-group C—X disconnection) outline the synthesis of the following target molecules:

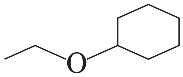
(a)


(b)


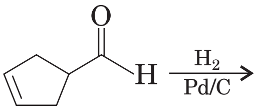
(c)


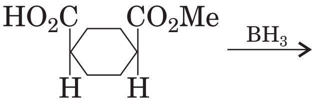
(d)


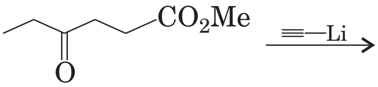
(e)


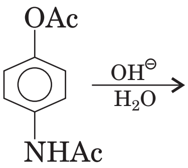
(f)


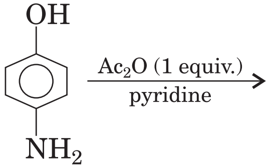
7. Predict the product and account for the chemoselectivity of the following reactions:

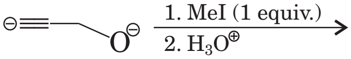
(a)


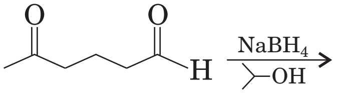
(b)


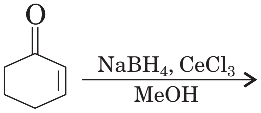
(c)


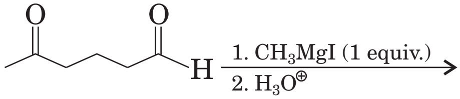
(d)


(e)


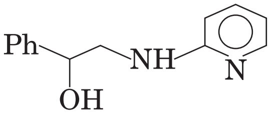
(f)


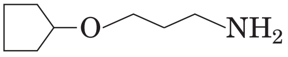
(g)


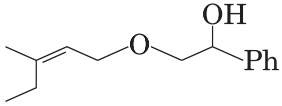
(h)


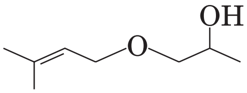
(i)


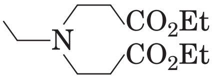
8. Outline the syntheses of the following target molecules with proper retrosynthetic analysis (involving two-group C—X disconnection):

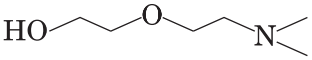
(a)


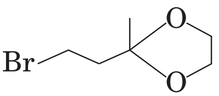
(b)


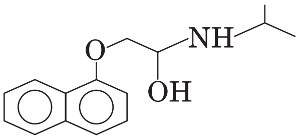
(c)


(d) 

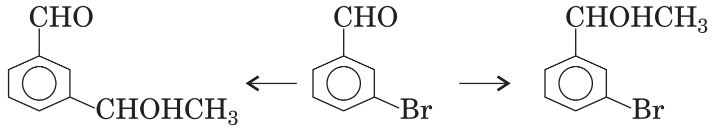
(e) 

(f) 

(g) 

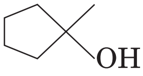
(h) 

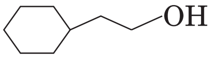
9. How would you convert *m*-bromobenzaldehyde(I) chemoselectively into two alcohols (II and III)?

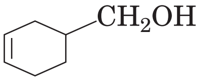


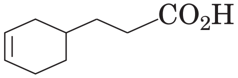
II I III

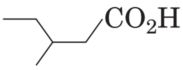
10. Using disconnection approach (one-group C—C disconnection), design a suitable synthesis for each of the following compounds:

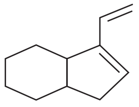
(a) 

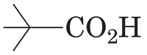
(b) 

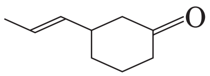
(c) 

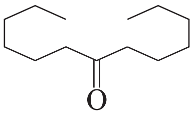
(d) 

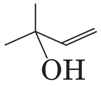
(e) 

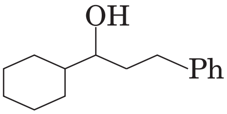
(f) 

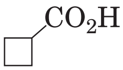
(g) 

(h) 

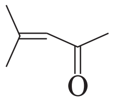
(i) 

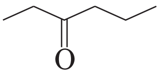
(j) 

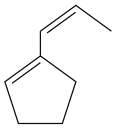
(k) 

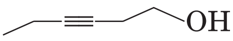
(l) 

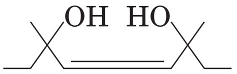
11. Using disconnection approach, design a suitable synthesis for each of the following target molecules (using acetylene):

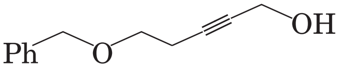
(a) 

(b) 

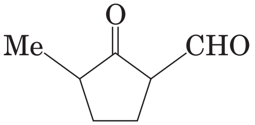
(c) 

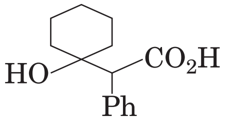
(d) 

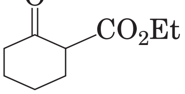
(e) 

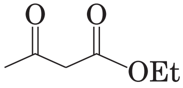
(f) 

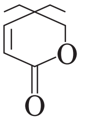
12. Describe the synthesis of the following target molecules with proper retrosynthetic analysis (involving two-group C—C disconnection):

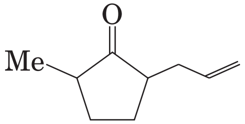
(a) 

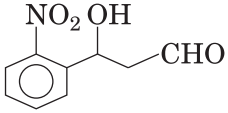
(b) 

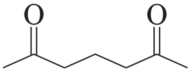
(c) 

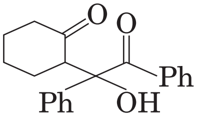
(d) 

(e) 

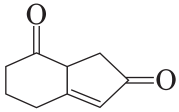
(f) 

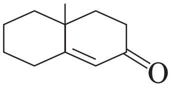
(g) 

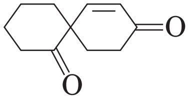
(h) 

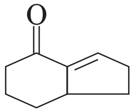
(i) 

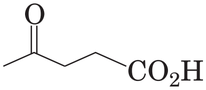
13. Outline the synthesis of each of the following target molecules with proper retrosynthetic analysis:

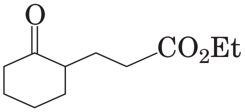
(a) 

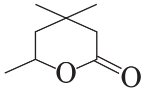
(b) 

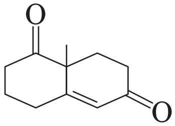
(c) 

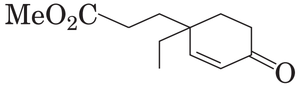
(d) 

(e) 

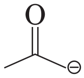
(f) 

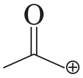
(g) 

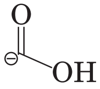
(h) 

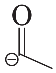
(i) 

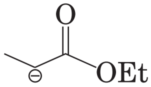
14. What is called *umpolung*? Explain with a suitable example. Label each of the following species as a normal synthon or an *umpolung* synthon:

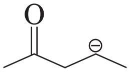
(a) 

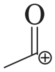
(b) 

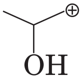
(c) 

(d) 

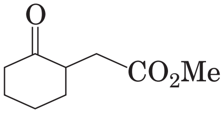
(e) 

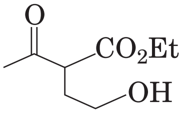
(f) 

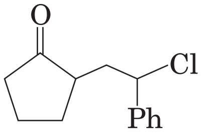
(g) 

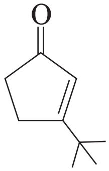
(g) 

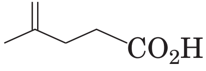
15. Using disconnection approach (illogical disconnection), design a suitable synthesis for each of the following compounds:

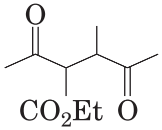
(a) 

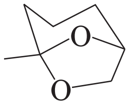
(b) 

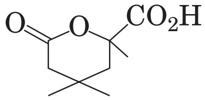
(c) 

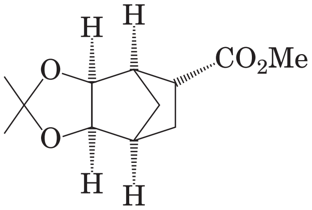
(d) 

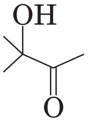
(e) 

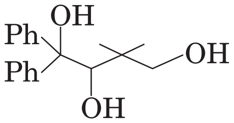
(f) 

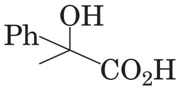
(g) 

(h) 

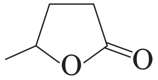
(i) 

(j) 

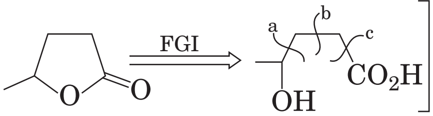
(k) 

(l) 

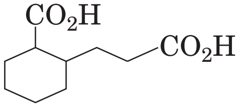
16. Give three syntheses of the following lactone with proper retrosynthetic analysis (considering all possible disconnections):

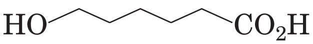


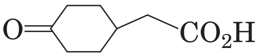
(a γ-lactone)

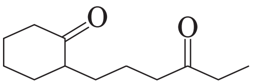
[**Hint:** ]

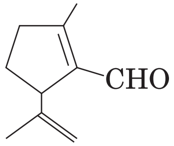
17. Outline the syntheses of the following target molecules with proper retrosynthetic analysis (involving reconnection):

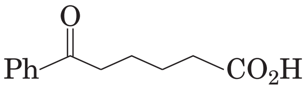
(a) 

(b) 

(c) 

(d) 

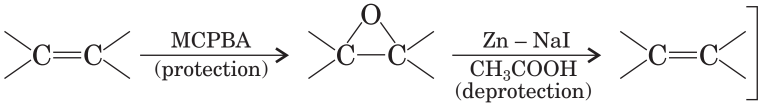
(e) 

(f) 

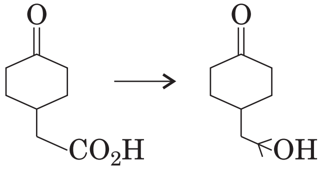
18. How would you carry out protection and deprotection of (i) terminal alkynes (an active C—H bond) and (ii) carbon—carbon double bond?

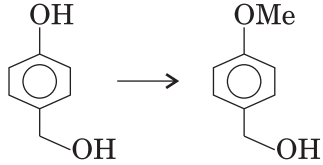
[**Hint:** (i) $R{-}C{\equiv}C{-}H \xrightarrow[\substack{-HCl\\ \text{(protection)}}]{TMS{-}Cl} R{-}C{\equiv}C{-}TMS \xrightarrow[\substack{2.\ KCN\\ \text{(deprotection)}}]{1.\ AgNO_3}$

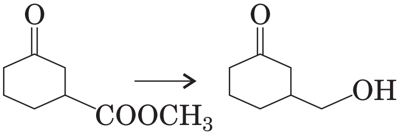
$$R{-}C{\equiv}CH \xleftarrow{H_2O} R{-}C{\equiv}C^{\ominus}K^{\oplus}$$

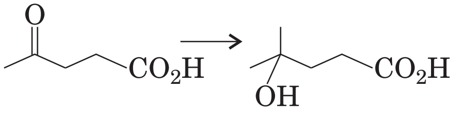
(ii) ]

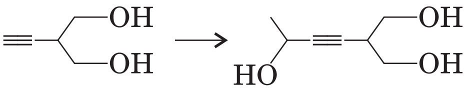
19. How would you carry out the following conversions using suitable protective groups wherever necessary?

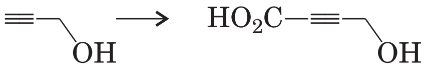
(a)


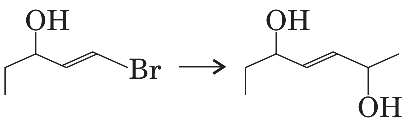
(b)


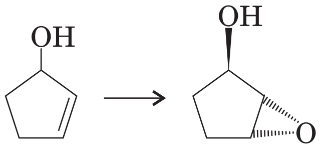
(c)


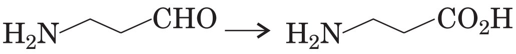
(d)


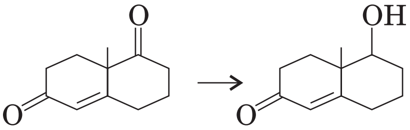
(e)


(f)


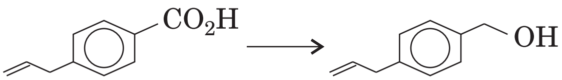
(g)


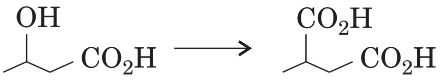
(h)


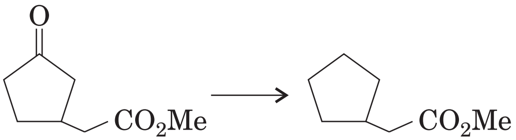
(i)


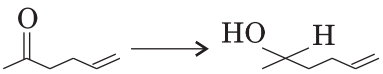
(j)


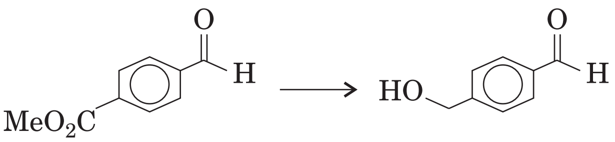
20. Presence of multiple functional groups in a compound does not always require protection for its chemical transformations and this is because chemoselective reagents can bring about the desired conversion. Carry out the following transformations using protection–deprotection strategy or suitable chemoselective reagents.

(a)


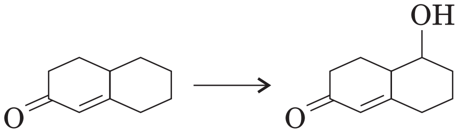
(b)


(c)


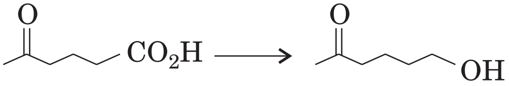
(d)


(e)


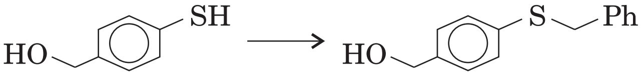
(f)



(g)



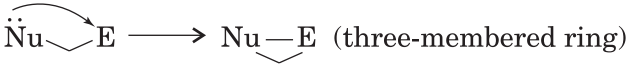
(h)

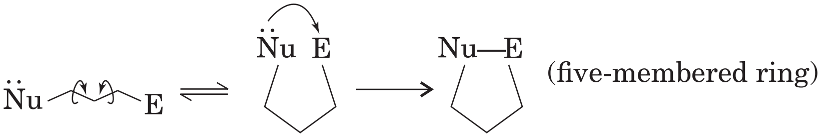


3.2 STRATEGY OF RING SYNTHESIS

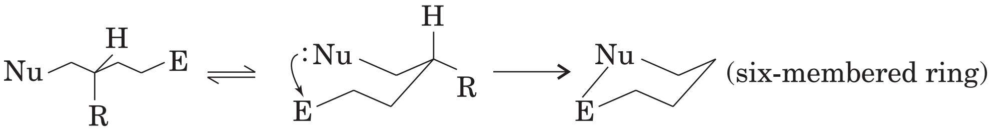
3.2.1 Thermodynamic and Kinetic Factors Involved in Ring Formation

Intramolecular reactions are generally favoured kinetically over intermolecular reactions for reasons of entropy because the two reactive sites are part of the same molecule (entropy loss is relatively small) and a bimolecular collision is not required. This favourable entropy factor is greatest in three-membered ring formation where the two ends of the substrates are always close, and for five-membered ring formation where natural thermal motion brings the reactive sites into bonding distance.

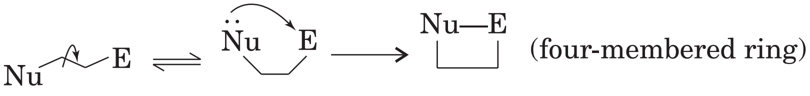




Six-membered ring formation takes places at a reasonable rate because in this case rotation brings the reactive sites very close to each other, and before bond formation, a folding of the chain is required.



The rate of four-membered ring formation is usually very slow, because even in the best conformation for cyclization (the *syn*-periplanar conformation), the reactive sites do not come into bonding distance.



The six-membered ring is, however, much favoured thermodynamically because it exists predominantly in chair conformation with all groups staggered (specially if large substituents occupy equatorial positions). Five-membered rings are also stable thermodynamically, but three- and four-membered rings are thermodynamically less stable and this is because they suffer from angle strain (bond angles of three- and four-membered rings are 60° and 90°, respectively, instead of the usual 109.5° for sp^3 and 120° for sp^2 atoms. The following table gives a summary of factors affecting formation of various sized rings.

Factors affecting ring formation

Size of the ring	Kinetic factors	Thermodynamic factors
Three-membered	✓✓✓	×
Four-membered	×	×
Five-membered	✓✓	✓
Six-membered	✓	✓✓

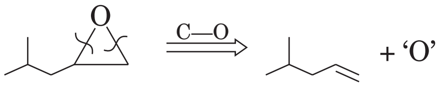
Taking both kinetic and thermodynamic factors into account, five- and six-membered rings are easy to make, and three-membered rings are also easy to make. However, they often break down again under the condition of their formation. Four-membered rings are difficult to make and often requires special methods.

3.2.2 Synthesis of Three-, Four-, Five- and Six-membered Saturated Heterocycles

3.2.2.1 Three-membered rings

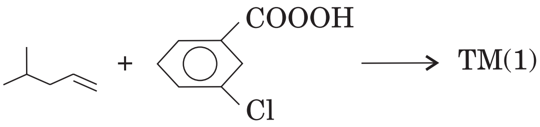
Most of the three-membered rings are synthesized by insertion reactions involving formation of two bonds in a single step. Epoxides are usually made from alkenes, hence both of the C—O bonds can be disconnected at once. The reagent for epoxidation is a peracid (e.g., MCPBA). The synthesis of the epoxide (1), for example, can be designed as follows.

Retrosynthetic analysis



TM(1)

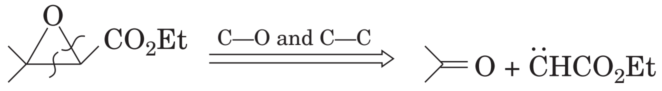
Synthesis



MCPBA

Disconnection of one C—C and one C—O bond suggests a carbene intermediate and this style of disconnection is important of the epoxides of α,β-unsaturated carbonyl compounds. The synthesis of the epoxide (2) can be designed as follows:

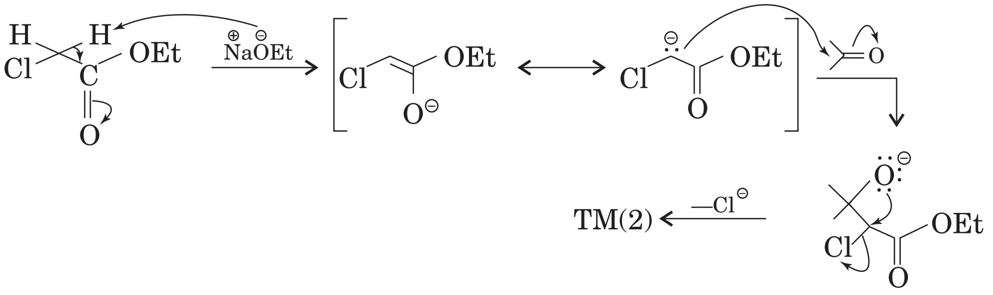
Retrosynthetic analysis



TM(2)

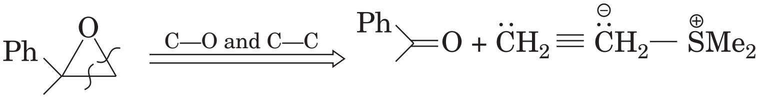
Synthesis

In the *Darzenes reaction* the halo ester $ClCH_2CO_2Et$ is used as a reagent for the carbene; a carbene is not actually an intermediate.



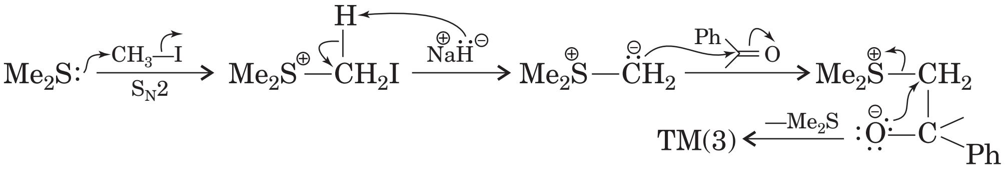
The same disconnection of a carbon atom is also helpful for epoxides containing no carbonyl substituent. The reagent here is a nucleophilic carbene equivalent, e.g., a sulphur ylide. The synthesis of the epoxide (3), e.g., can be designed as follows.

Retrosynthetic analysis



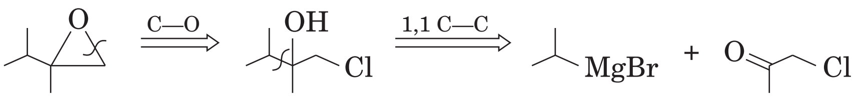
TM(3)

Synthesis



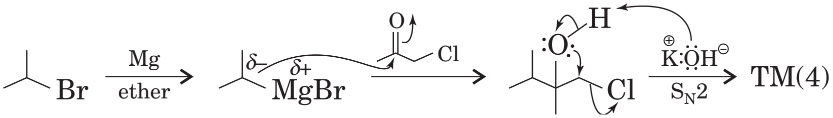
One C—O disconnection followed by a C—C disconnection leads to an *α*-chloro ketone (a good starting material). The synthesis of the epoxide (4), e.g., can be designed as follows.

Retrosynthetic analysis



TM(4)

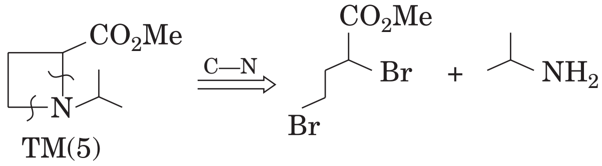
Synthesis



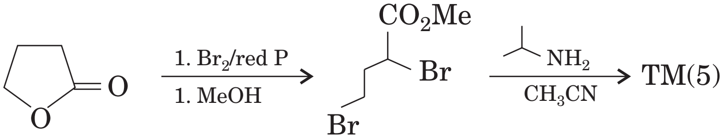
3.2.2.2 Four-membered rings

It is much difficult to make four-membered rings. The normal cyclisation process often give poor results but is sometimes successful. Straightforward C—N disconnection of a cyclic amine suggests a 1,3-dibromide as the starting material which can be prepared from a readily available lactone. The synthesis of the cyclic amine (5), for example, can be designed as follows.

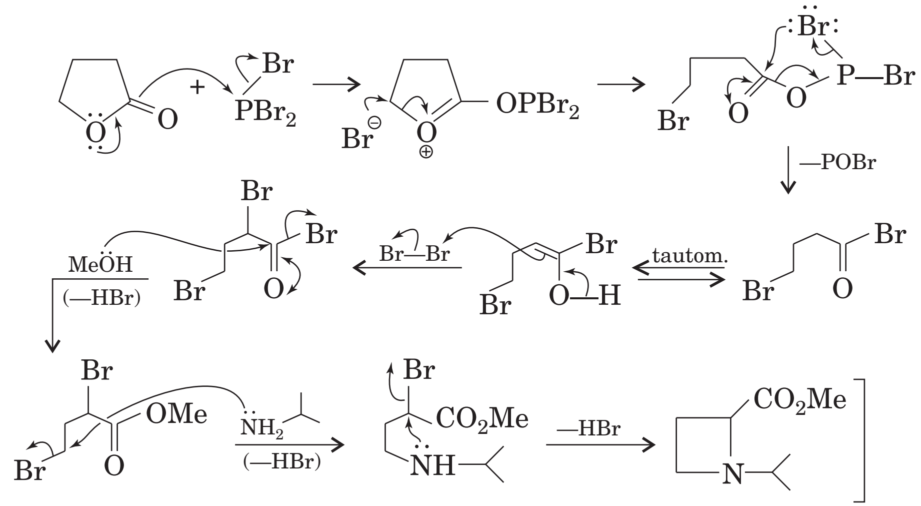
Retrosynthetic analysis



Synthesis

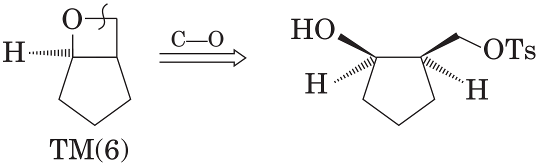


Mechanism:

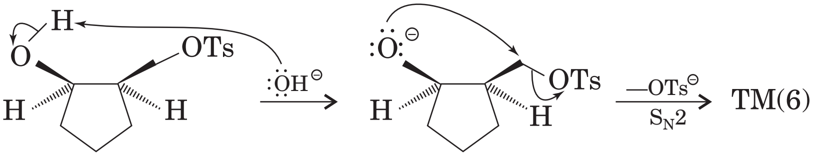


In much favourable cases, four-membered cyclic ethers can also be prepared by cyclisation. Disconnection of one C—O bond leads to a 1,3-diol of which the primary alcoholic group is converted into a good leaving group. The synthesis of the cyclic ether (6), for example, can be designed as follows.

Retrosynthetic analysis

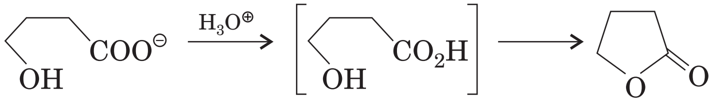


Synthesis



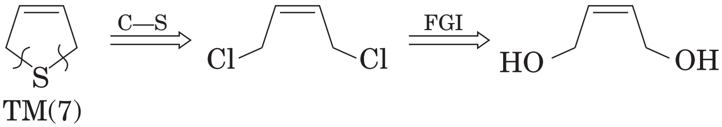
3.2.2.3 Five-membered rings

Due to both kinetic and thermodynamic advantages, five-membered rings are easiest to make by cyclisation reaction. Hydroxy acids, for example, cannot usually be isolated. Although the carboxylate ion is stable, on acidification, it undergoes ready cyclisation to yield lactones.

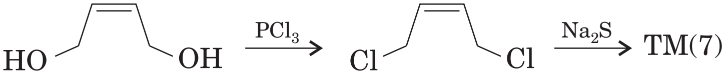


The strategy for the synthesis of five-membered heterocycles involves disconnection of both the C—X bonds and identification of the electrophilic carbon fragment needed to add to the nucleophilic heteroatom. The synthesis of the cyclic sulphide (7), for example, can be designed as follows. It requires a *cis*-dihalide which comes from *cis*-butenediol.

Retrosynthetic analysis

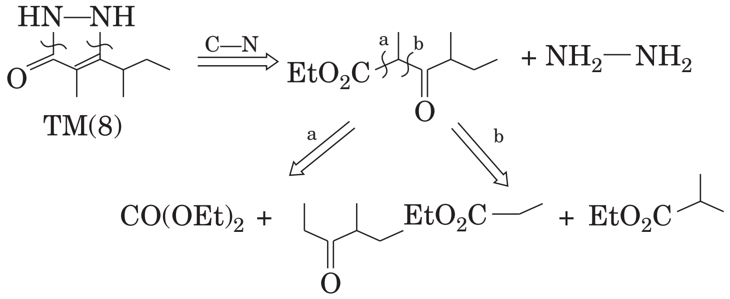


Synthesis



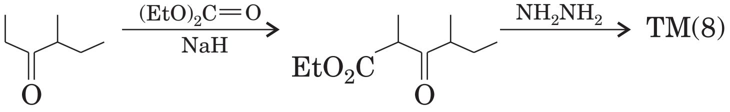
It is often very much easy to identify a readily available fragment when there are two heteroatoms in the ring. Disconnection of the following target molecule (8) reveals hydrazine and a keto ester.

Retrosynthetic analysis



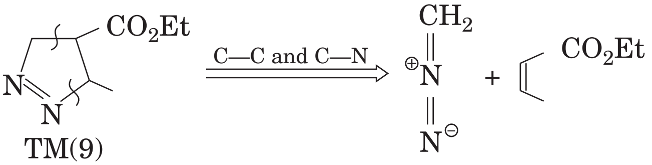
Disconnection (b) is ambiguous as one of the esters can self-condense. Disconnection (a), on the other hand, is not ambiguous as only the required product can form a stable enolate ion.

Synthesis

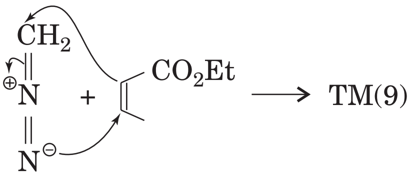


1,3-Dipolar cycloaddition is a special method for the synthesis of five-membered rings. This is like a Diels-Alder reaction with the diene replaced by a three atom 1,3-dipolar system (a four electron unit). The synthesis of the compound (9), for example, can be designed as follows.

Retrosynthetic analysis

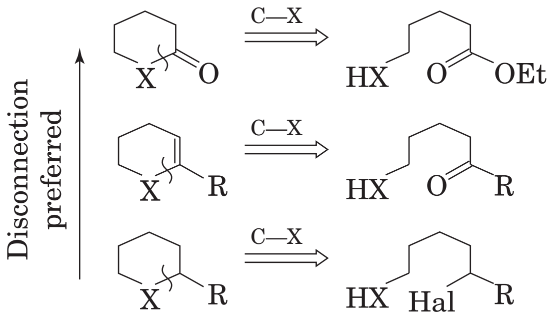


Synthesis



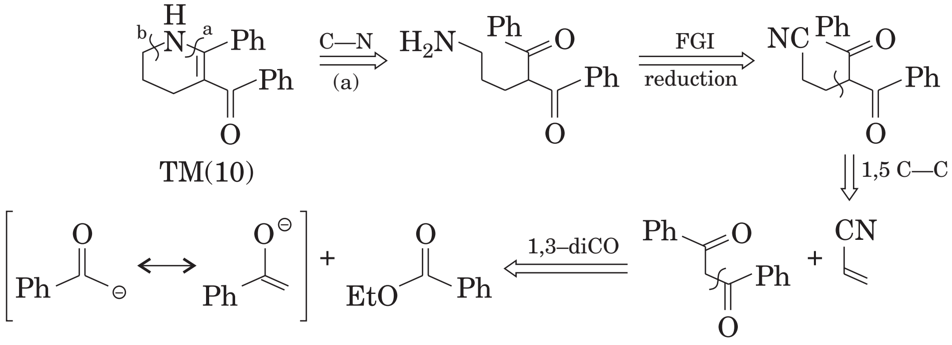
3.2.2.4 Six-membered rings

Cyclisation reactions can be employed for the synthesis of six-membered rings since both entropy and kinetic factors favour their formation. Where the heteroatom is bonded to carbon atoms at different oxidation levels, the best order of events is to disconnect X—C═O first and X—C_{sp^3} last.

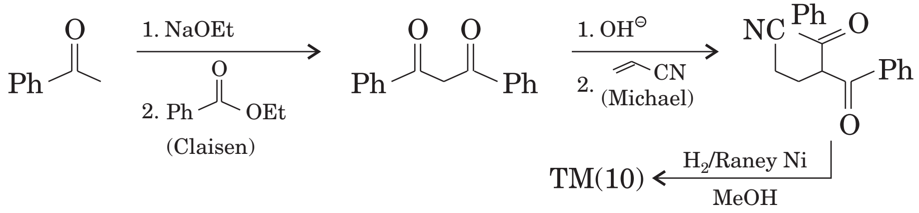


If this order of events is followed, disconnection (a) on the target molecule (10) should come first. This reveals a symmetrical amino ketone. Disconnection of the C—C bond after an FGI gives simpler starting compounds.

Retrosynthetic analysis

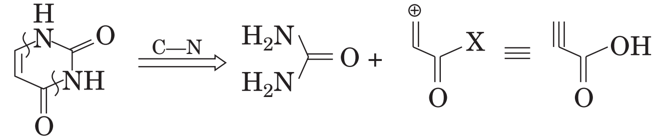


Synthesis



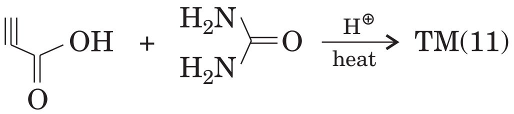
When a ring contains two heteroatoms, it is useful to look for a fragment containing both of them. The nucleic acid base uracil, for example, can be disconnected to urea and a suitable electrophilic fragment. Michael addition to an electrophilic acetylene is a suitable reaction in this case.

Retrosynthetic analysis



TM(11)
(Uracil)

Synthesis

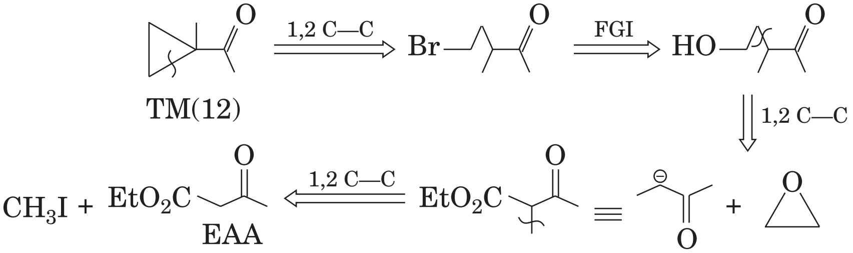


3.2.3 Synthesis of Three, Four-, Five- and Six-membered Carbocyclic Rings

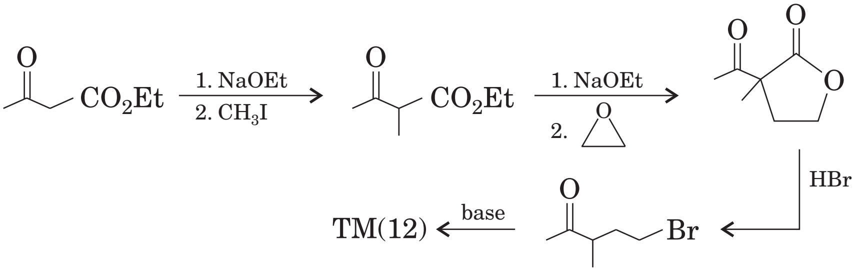
3.2.3.1 Three-membered rings

Since the alkylation of carbonyl compounds is generally irreversible and kinetically favourable, it yields three-membered rings without control. The synthesis of the cyclopropyl ketone (12), for example, can be designed as follows.

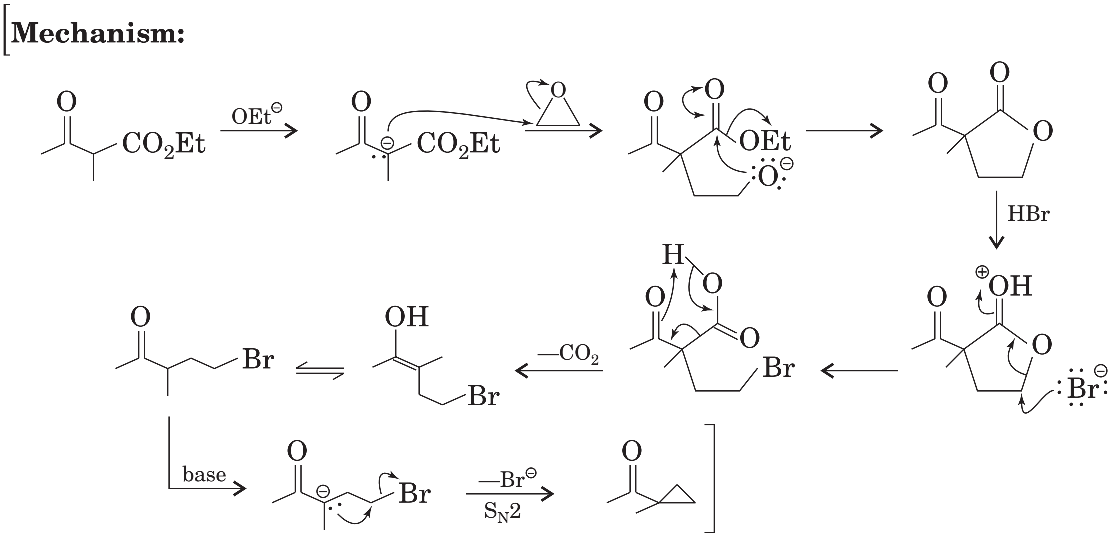
Retrosynthetic analysis



Synthesis

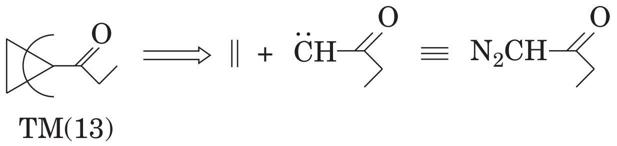


Mechanism:

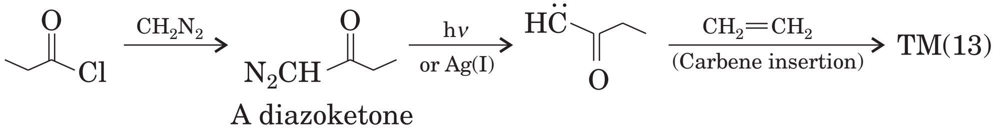


A reagent for a carbene with one carbonyl group is required for a similar disconnection of cyclopropyl ketones. This can be supplied as a diazoketone obtained from acid chloride and diazomethane. The synthesis of the cyclopropyl ketone (13), for example, can be designed as follows.

Retrosynthetic analysis

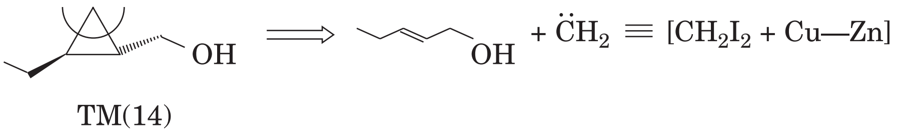


Synthesis

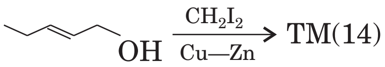


The best carbene source is CH_2I_2 with zinc-copper couple, i.e., ICH_2ZnI (a *carbenoid*) used in *Simmons–Smith reaction*. Because of H-bonding, the reagent is much effective when reacts with allylic alcohols. The reaction is stereoselective. The synthesis of the alcohol (14), for example, can be designed as follows.

Retrosynthetic analysis

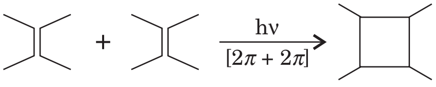


Synthesis



3.2.3.2 Four-membered Rings

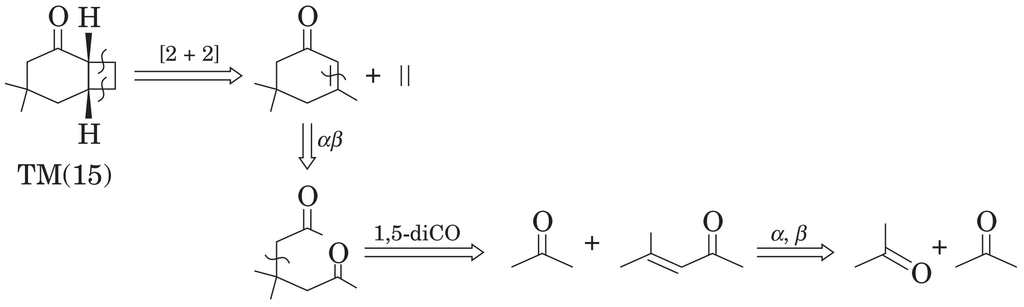
A special method involving photochemical [2 + 2] cyclo-addition reaction is often used to synthesize four-membered rings which are difficult to be formed.



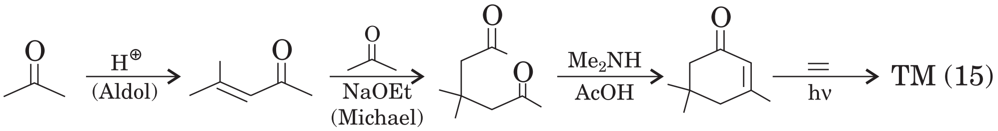
(a pericyclic reaction)

The reaction takes place smoothly when one alkene conjugated like an enone. The synthesis of the bicyclic compound (15), for example, can be designed as follows.

Retrosynthetic analysis

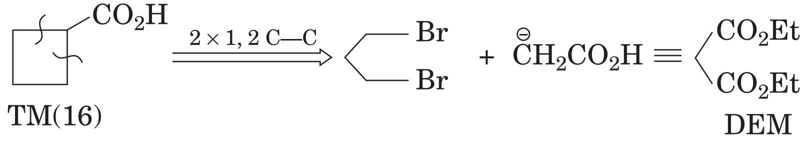


Synthesis

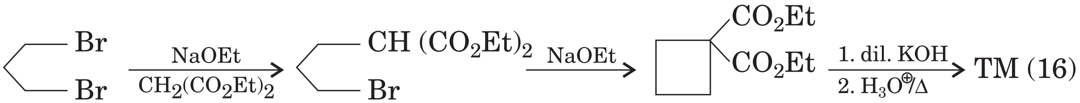


There are some rare ionic reactions which are also useful for the synthesis of four-membered rings. The target molecule (16) and (17), for example, can be synthesized from readily available starting materials like diethyl malonate (DEM) and adipic acid, respectively.

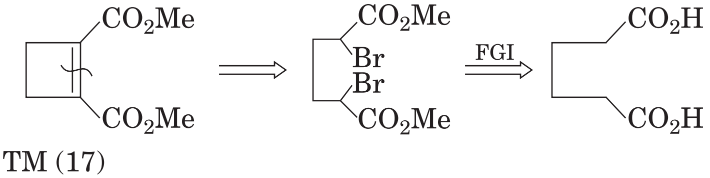
Retrosynthetic analysis



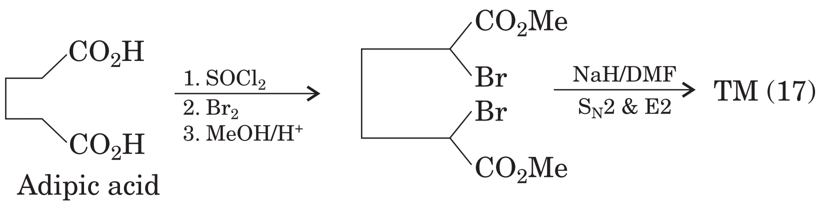
Synthesis



Retrosynthetic analysis

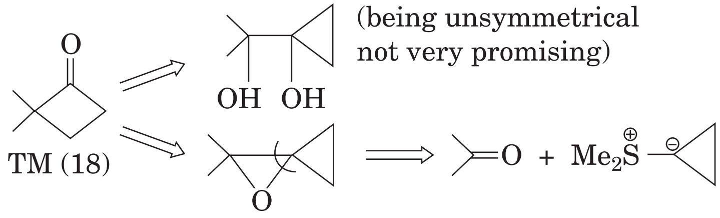


Synthesis



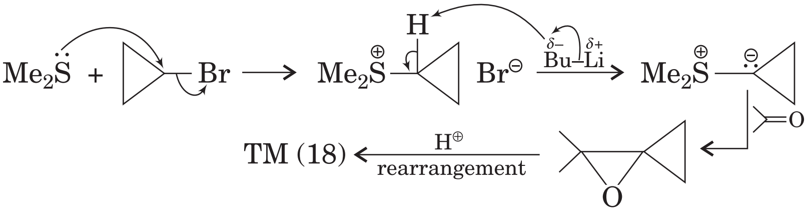
An alternative method for synthesizing four-membered rings involves ring expansion of the strained three-membered rings. Release of some strain (60° → 90°) is actually the driving force for the reaction. The synthesis of 2,2-dimethylcyclo-butanone (18), for example, can be designed as follows.

Retrosynthetic analysis

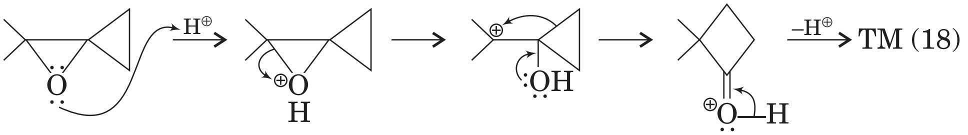


(being unsymmetrical not very promising)

Synthesis



[*Mechanism of the rearrangement step:*

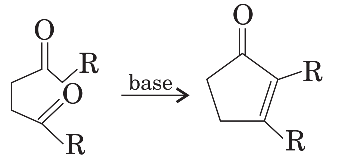


]

3.2.3.3 Five-membered rings

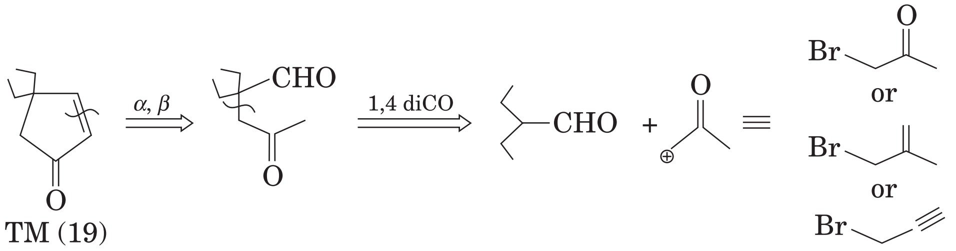
Since the formation of five-membered rings is favourable both kinetically and thermodynamically, these can be easily synthesized by conventional methods (making use of carbonyl chemistry) as follows:

(a) Using 1,4-dicarbonyl compounds Carbonyl condensation involving 1,4-dicarbonyl compounds is one of the potential routes to five-membered rings. This is often called cyclopentaannelation.



The synthesis of the cyclopentanone (19) with proper retrosynthetic analysis may be given as follows.

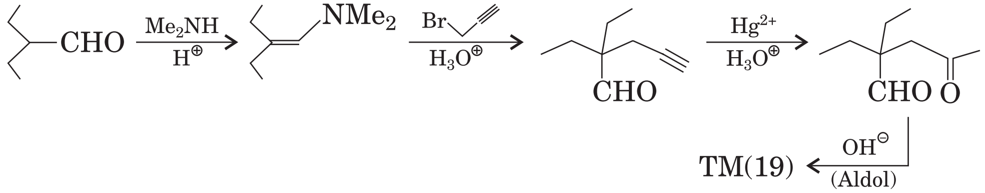
Retrosynthetic analysis



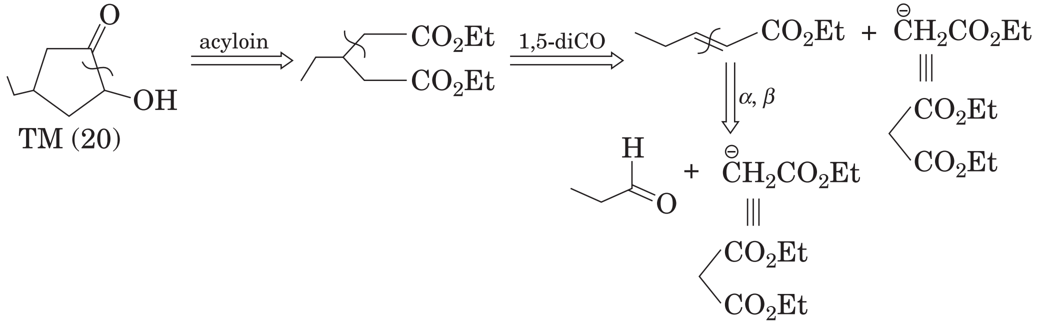
TM (19)

The enamine of the aldehyde is used to ensure control

Synthesis

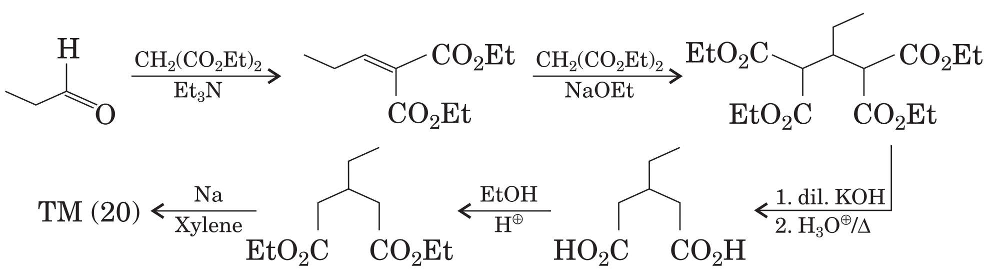


(b) Using 1,5-dicarbonyl compounds Five-membered rings can be synthesized from 1,5-diesters by acyloin condensation in the presence of trimethylsilyl chloride (to protect the oxygen-sensitive ene-diol). The retrosynthetic analysis and the designed synthesis of the acyloin (20), for example, may be outlined as follows.



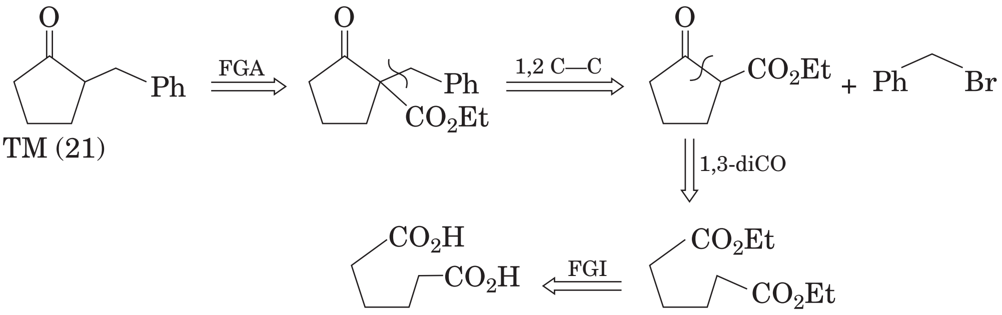
TM (20)

Synthesis

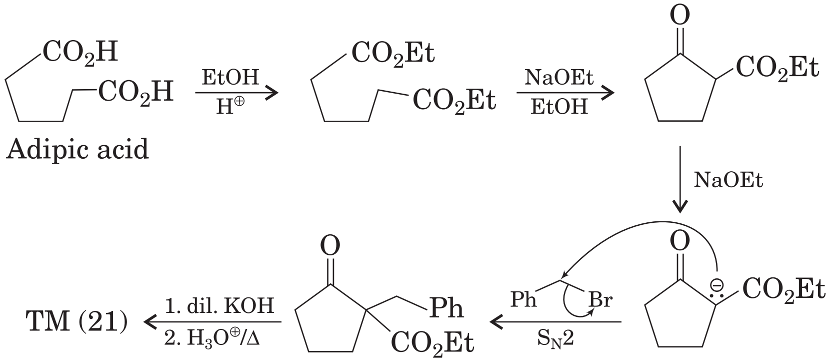


(c) Using 1,6-dicarbonyl compounds Cyclopentanone and its 2-alkyl derivatives can be synthesized from adipic ester (a 1,6-dicarbonyl system) and hence, from adipic acid. Synthesis of 2-benzylcyclopentanone (21), for example, can be designed as follows.

Retrosynthetic analysis



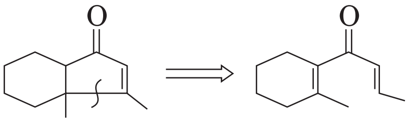
Synthesis



Five-membered rings can also be prepared by pericyclic reactions.

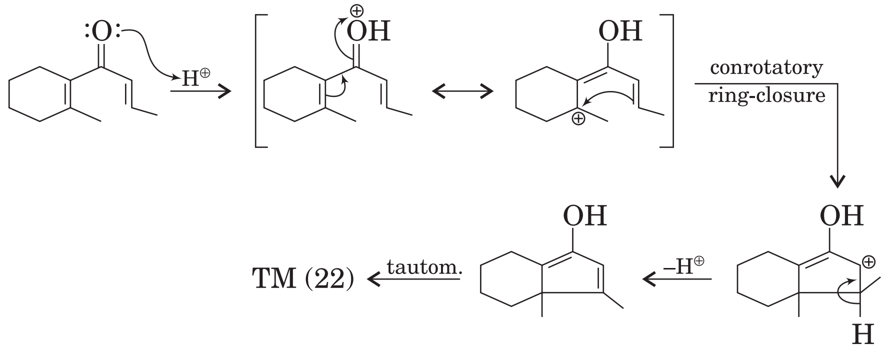
(a) Using electrocyclic reactions Pentadienyl cations undergo thermal cyclization to cyclopentenyl cations in a conrotatory fashion (a symmetry allowed process involving 4π electron system). Cyclopentenones can be synthesized from dienones by applying this approach. The synthesis of the cyclopentenone (22), for example, can be designed as follows.

Retrosynthetic analysis

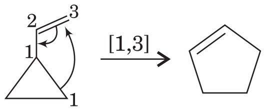


TM (22)

Synthesis

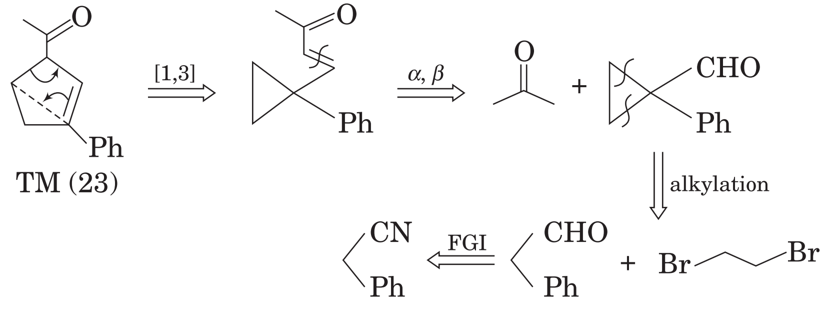


(b) Using sigmatropic rearrangements Vinylcyclopropanes rearranges to give cyclopentenes when heated. This [1,3] sigmatropic shift is a disallowed process. Even though it occurs because the reaction is very favourable in enthalpy terms.

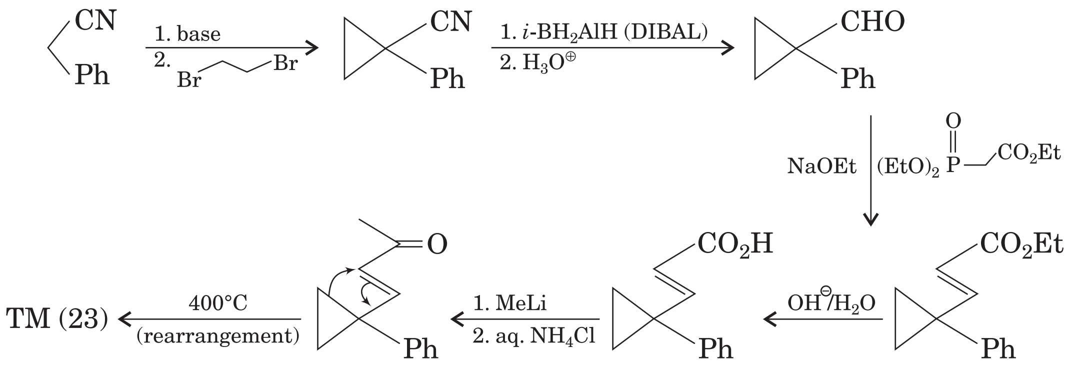


The usual way to see the disconnection is to reverse the reaction. The retrosynthetic analysis and the designed synthesis of the cyclopentanone (23) may be outlined as follows.

Retrosynthetic analysis



Synthesis



3.2.3.4 Six-membered rings

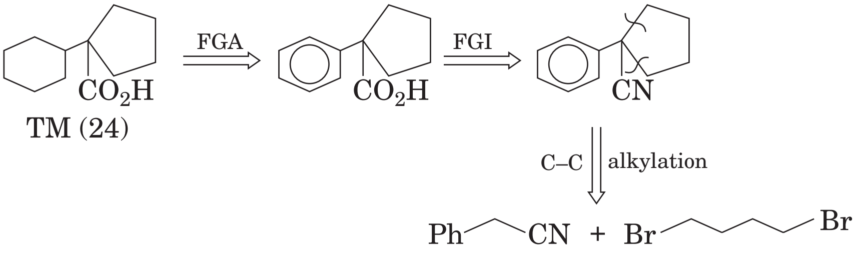
The three general methods for synthesizing aliphatic six-membered rings are as follows:

- (a) Diels–Alder reaction
- (b) Carbonyl condensations (*Robinson annelation*)
- (c) Reduction of aromatic compounds: (i) total reduction and (ii) partial reduction (Birch reduction)

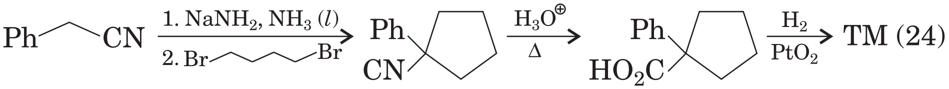
[For (a) and (b), see sections 3.1.10.1 and 3.1.10.3, respectively]

A benzene derivative can be totally reduced to a cyclohexane ring in the presence of an active catalyst under pressure. The synthesis of the acid (24), for example, can be designed as follows.

Retrosynthetic analysis

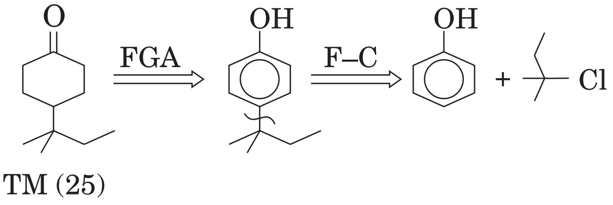


Synthesis

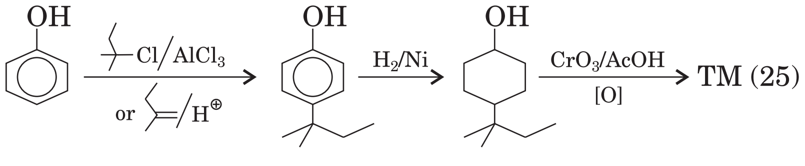


A cyclohexane ring with two remote substituents can be synthesized from a *para* disubstituted aromatic compound which, in turn, can easily be synthesized from a monosubstituted compound by making use of the directing influence of the substituent already present. The synthesis of the ketone (25) with proper retrosynthetic analysis may be outlined as follows.

Retrosynthetic analysis

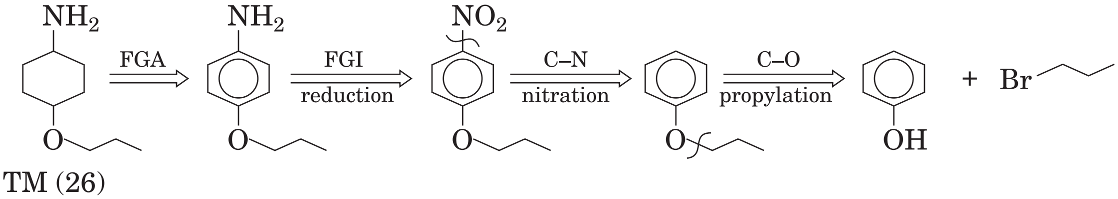


Synthesis

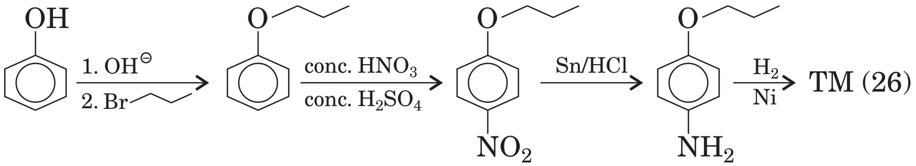


As C—N disconnection is obvious in aromatic compounds but not in aliphatic compound, this type of approach becomes very useful in the synthesis of amine derivatives. The synthesis of the amine (26), for example, can be designed as follows.

Retrosynthetic analysis

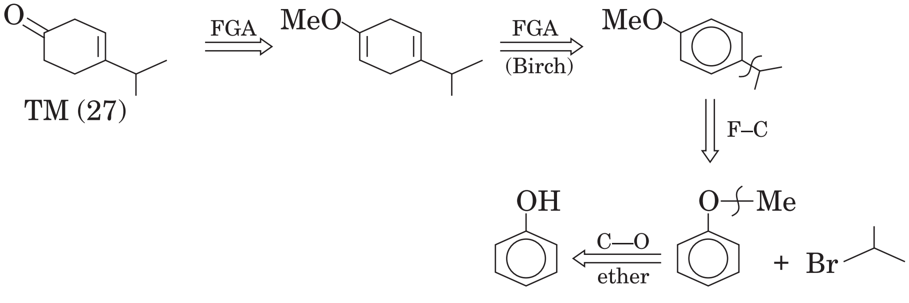


Synthesis

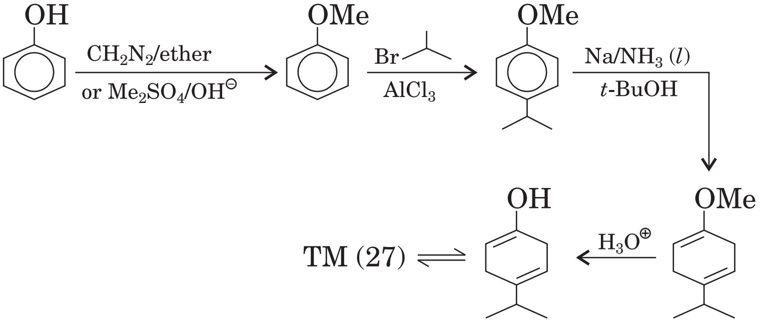


In Birch reduction, partial reduction of aromatic compounds leading to the formation of non-conjugated dienes takes place. In the product, the electron-withdrawing substituent remains attached with the saturated carbon atom while electron-releasing substituent remains attached with the double-bonded carbon. The most useful application of this method is that the substituents present in a six-membered ring can be easily introduced in the aromatic ring because of right orientations. The retrosynthetic analysis and an efficient synthesis of the ketone (27) may be outlined as follows.

Retrosynthetic analysis

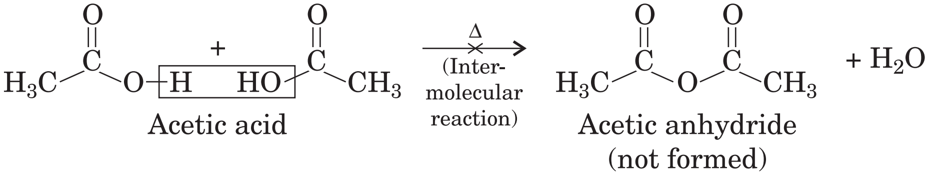


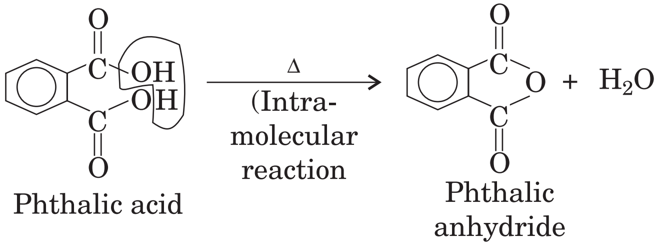
Synthesis



3.2.4 Synthesis of Large Rings: Applicaton of High Dilution Technique

When acetic acid is heated, no intermolecular reaction occurs to form acetic anhydride. However, when phthalic acid is heated, it undergoes intramolecular reaction readily to yield phthalic anhydride.





In fact, an intramolecular reaction is both thermodynamically and kinetically more favourable than an intermolecular reaction. This can be explained as follows:

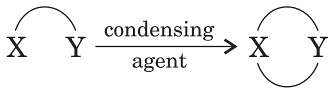
(i) Thermodynamic preference In an intermolecular reaction, two product molecules are formed from every two reactant molecules. As a consequence, the amount of disorder, i.e., the entropy of the system remains almost unchanged. However, in an intramolecular reaction, two product molecules are formed from one reactant molecule. Consequently, the amount of disorder, i.e., the entropy of the system increases. Thus, an intramolecular reaction is entropically favourable than an intermolecular reaction. The formation of acetic anhydride, for example, is entropically unfavourable ($\Delta S^\circ \approx 0$), whereas the formation of phthalic anhydride is entropically favourable (ΔS° = +ve). Since $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$, ΔG° in an intramolecular reaction is more negative than that of an intermolecular reaction and therefore, an intramolecular reaction is thermodynamically more favourable than an intermolecular reaction.

(ii) Kinetic preference The kinetic preference of a reaction is related to the activation energy ($\Delta G^\ddagger$) of the reaction. If $\Delta G^\ddagger$ is more positive, the transition state is less stable and the reaction occurs at a slower rate. However, if $\Delta G^\ddagger$ is less positive, the transition state is more stable and the reaction takes place at a faster rate. Now, in an intermolecular reaction, two separate molecules form the single activated complex or transition state leading to a larger decrease in entropy of activation, i.e. $\Delta S^\ddagger$ is more negative for an intermolecular reaction. However, in the case of an intramolecular reaction, $\Delta S^\ddagger$ is less negative as a single molecule forms a single activated complex. Now, $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$. Therefore, $\Delta G^\ddagger$ of an intermolecular reaction is more positive than that of an intramolecular reaction. So, an intramolecular reaction is kinetically more preferred over an intermolecular reaction.

However, when a large ring compound is synthesized from an α, ω-bifunctional compound, the flexibility of the molecule decreases largely on going from the reactant to the product. Thus, ΔS° is not so positive and therefore, such an intramolecular reaction is thermodynamically less favourable. Also, the flexibility of the molecule decreases largely on going from reactant to the activated complex. Thus, $\Delta S^\ddagger$ is more negative and therefore, such an intramolecular reaction is also kinetically less favourable. Therefore, some problem arises in synthesizing large ring compounds and this can be solved by the 'High Dilution Technique'.

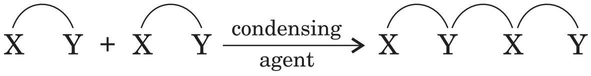
According to the *high dilution principle*, by using sufficiently dilute solution of a substrate (acyclic precursors like diester, dicyanide, bromo acid, acyl chloride of benzene derivatives, etc.), the distance between different molecules can be made greater than the distance between the two functional groups of the same molecule. As a result, cyclic compound is formed instead of linear condensation product (a likely result in concentrated solution).

An intramolecular reaction:



Now, the rate of the reaction = $k_{\text{intra}} \times [\overset{\frown}{X\quad Y}] \times [\text{condensing agent}]$

An intermolecular reaction:



Now, the rate of the reaction = $k_{\text{intra}} \times [\overset{\frown}{X\quad Y}]^2 \times [\text{condensing agent}]$

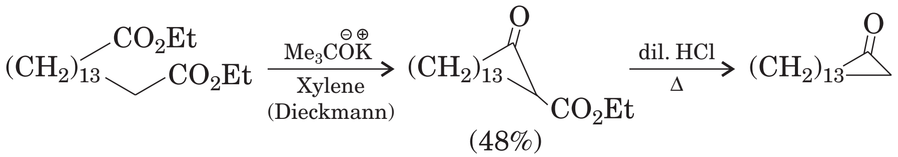
$$\therefore \quad \frac{\text{Rate of the intramolecular reaction}}{\text{Rate of the intermolecular reaction}} = \frac{k_{\text{intra}}}{k_{\text{inter}}} \times \frac{1}{[\overset{\frown}{X—Y}]}$$

Therefore, a low concentration of the substrate is expected to favour the intramolecular reaction.

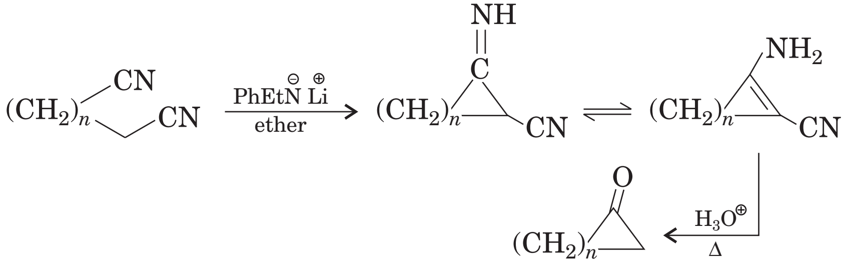
The high dilution technique involves introduction of the acyclic precursor very slowly into the reaction medium so that its concentration is always very low 10^{-3}(M) or less. At this concentration, the probability of intermolecular reaction is greatly reduced as the molecules then remain far apart from each other. Under such high dilution conditions, Dickmann or related reactions give acceptable yields of medium and large ring compounds.

Examples of syntheses carried out by high dilution technique:

1. Synthesis of ketone from diester:



2. Synthesis of ketone from dicyanide:

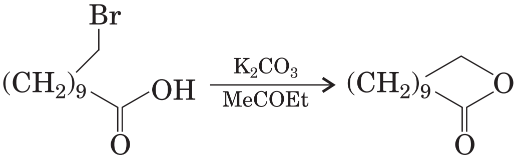


$(CH_2)_n$
CN
CN
$\text{PhEt}\overset{\ominus}{\text{N}}\,\overset{\oplus}{\text{Li}}$
ether
NH
C
NH$_2$
$H_3O^\oplus$
Δ
O

n = 5, 95% yield
n = 6, 88% yield
n = 12, 60–80% yield

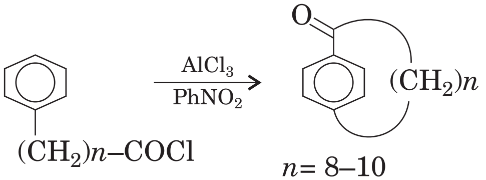
Since $\text{PhEt}\overset{\ominus}{\text{N}}\overset{\oplus}{\text{Li}}$ is a highly hindered base, its reaction as a nucleophile with the –CN group is minimised.

3. Synthesis of lactone from bromoacid:



(85%)

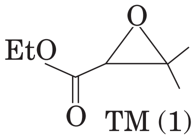
4. Aromatic ketone from acyl chloride by Friedel-Craft reaction:



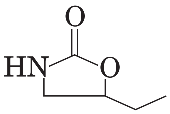
n= 8–10

SOLVED PROBLEMS

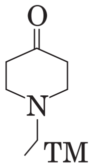
1. **Outline the synthesis of the following target molecules with proper retrosynthetic analysis.**

(a)


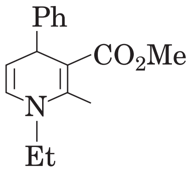
TM (1)

(b)


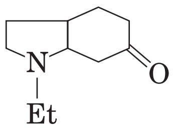
TM (2)

(c)


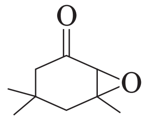
TM (3)

(d)


TM (4)

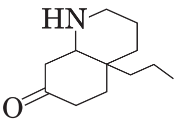
(e)


TM (5)

(f)


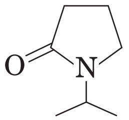
TM (6)

(g)



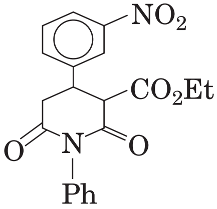
TM (7)

(h)



TM (8)

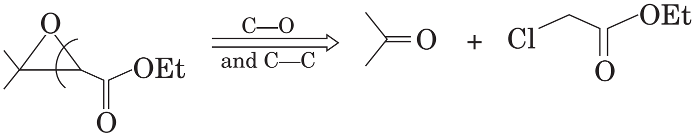
(i)



TM (9)

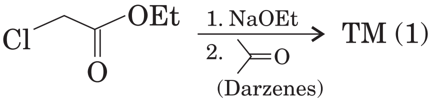
Solution

(a) *Retrosynthetic analysis*

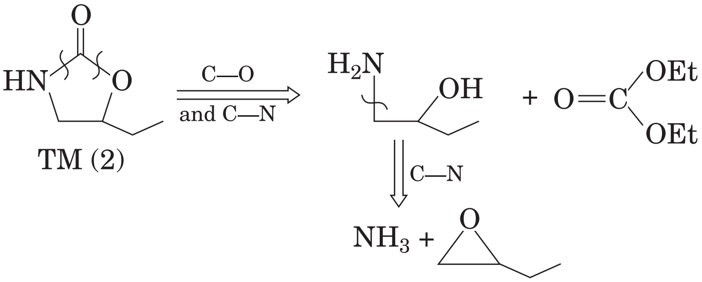


TM (1)

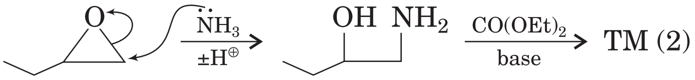
Synthesis



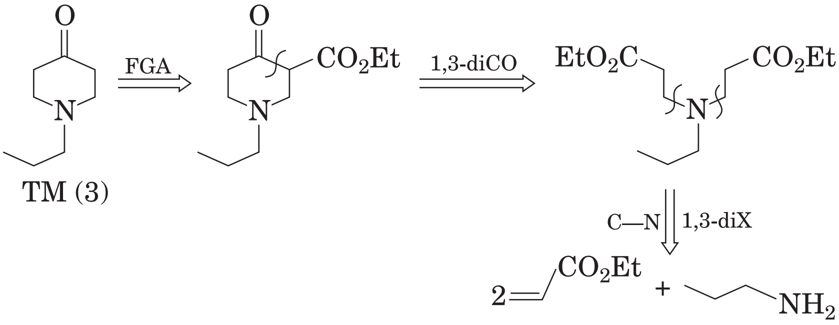
(b) *Retrosynthetic analysis*



Synthesis

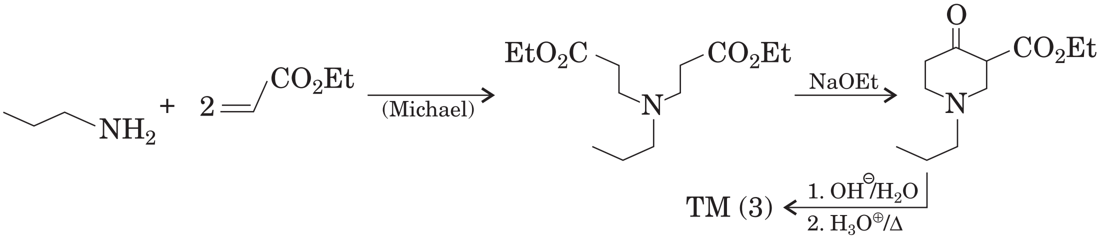


(c) *Retrosynthetic analysis*

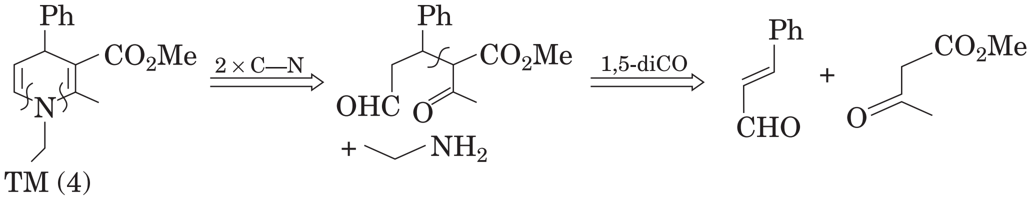


Because of ready availability of the starting materials (benzyl amine and ethyl acrylate), the synthesis is easy and straight forward.

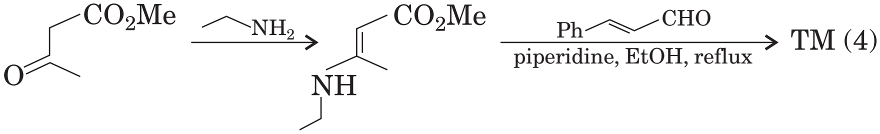
Synthesis



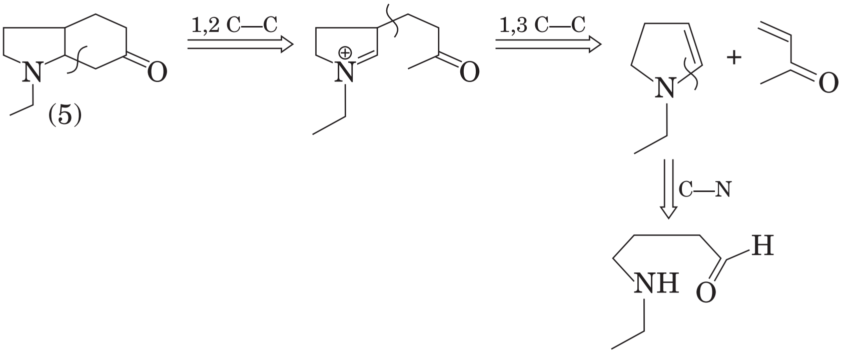
(d) *Retrosynthetic analysis*



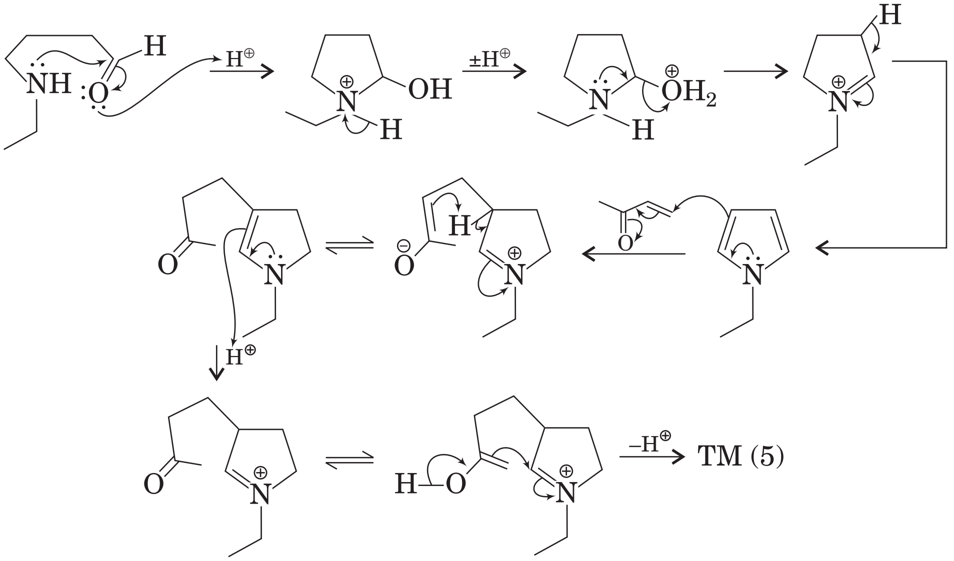
Synthesis



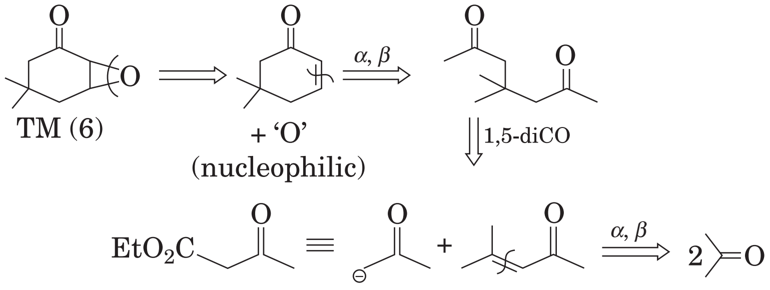
(e) *Retrosynthetic analysis*



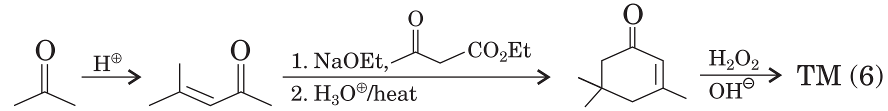
Synthesis



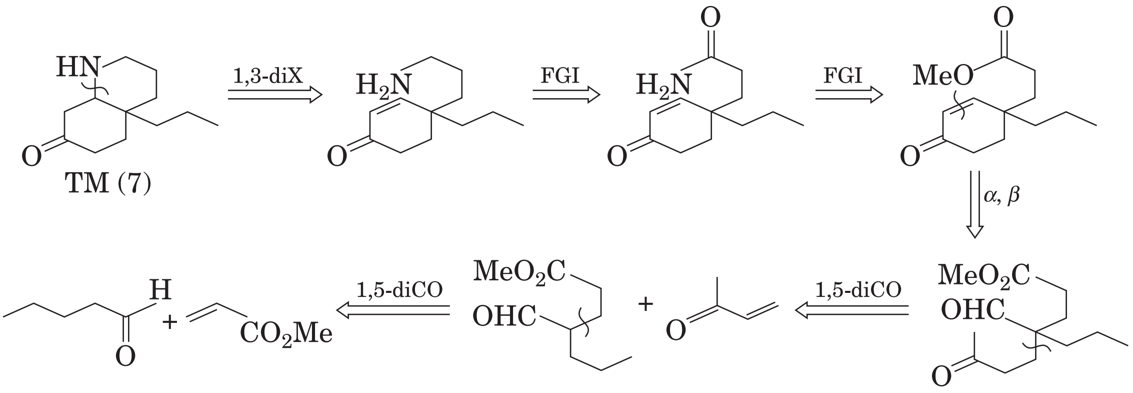
(f) *Retrosynthetic analysis*



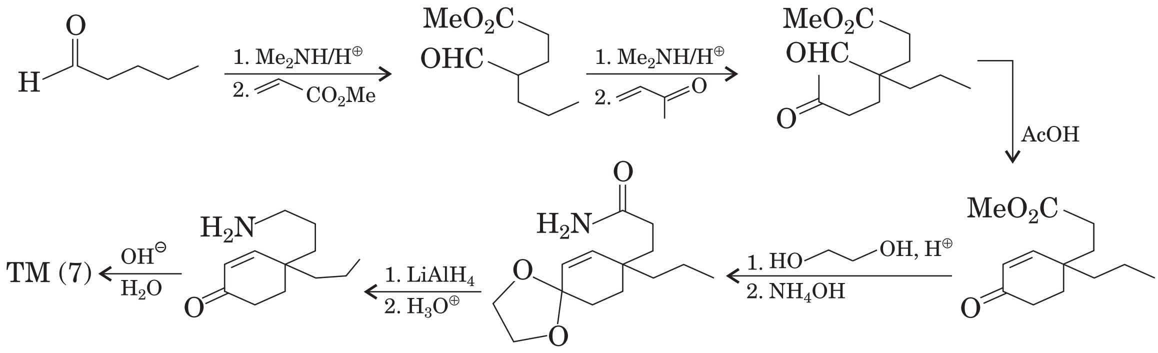
Synthesis



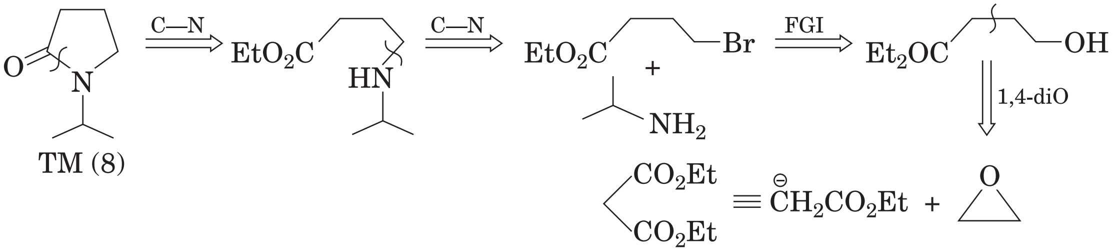
(g) *Retrosynthetic analysis*



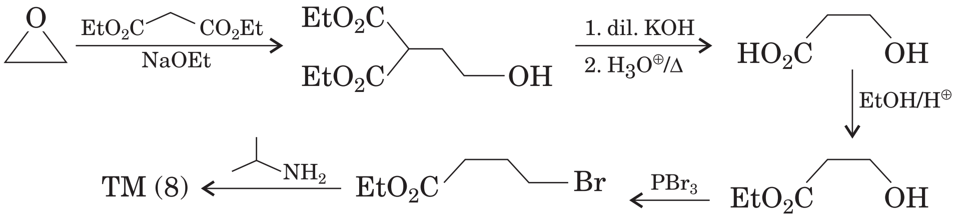
Synthesis



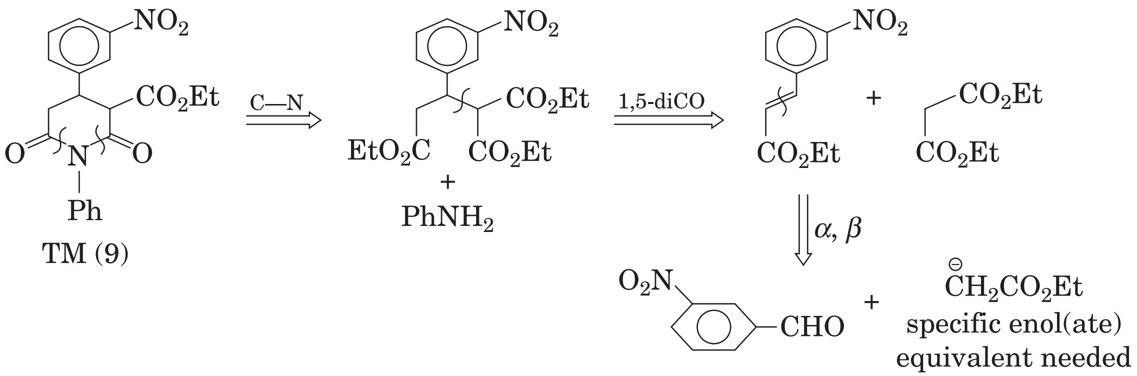
(h) *Retrosynthetic analysis*



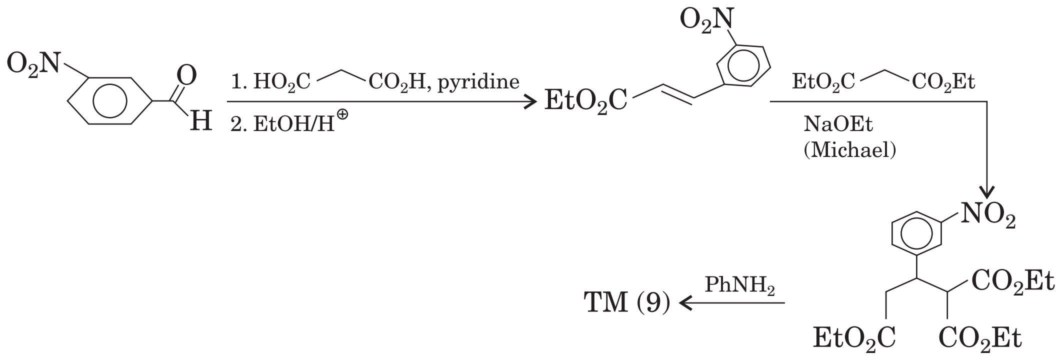
Synthesis



(i) *Retrosynthetic analysis*



Synthesis



2. Using disconnection approach, design a suitable synthesis for each of the following target molecules:

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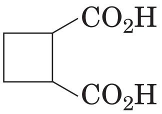
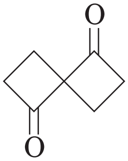
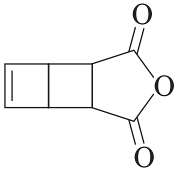


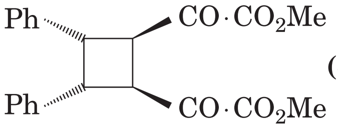
TM (10)

(b)


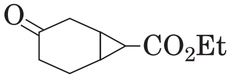
TM (11)

(c)


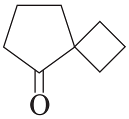
TM (12)

(d)


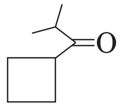
TM (13)

(e)


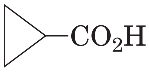
TM (14)

(f)


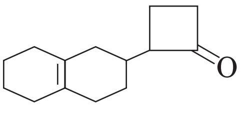
TM (15)

(g)


TM (16)

(h)


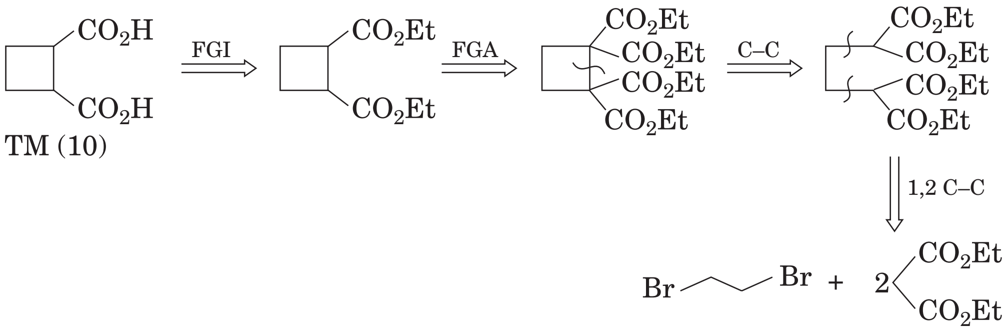
TM (17)

(i)


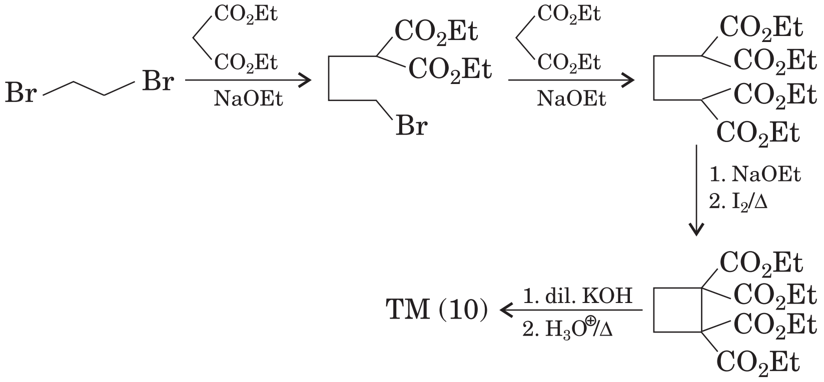
TM (18)

Solution

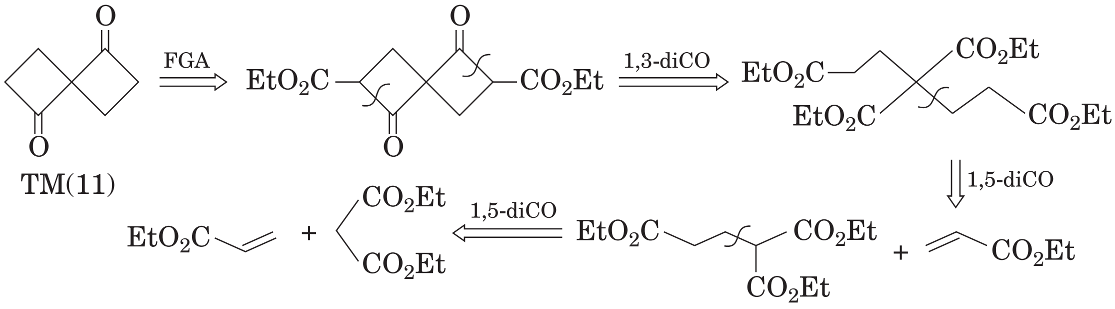
(a) *Retrosynthetic analysis*



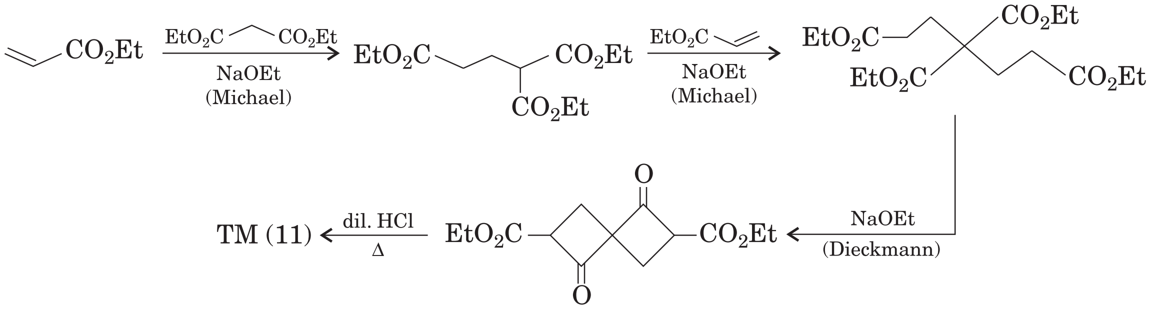
Synthesis



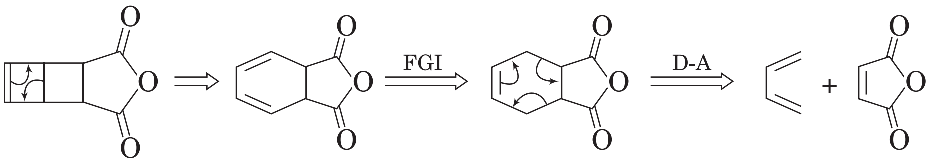
(b) *Retrosynthetic analysis*



Synthesis

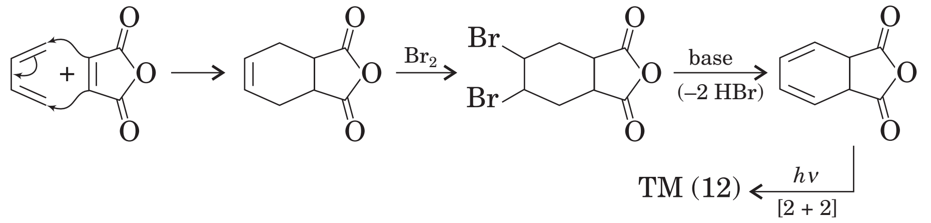


(c) *Retrosynthetic analysis*

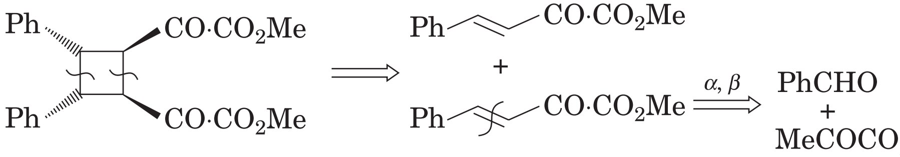


TM (12)

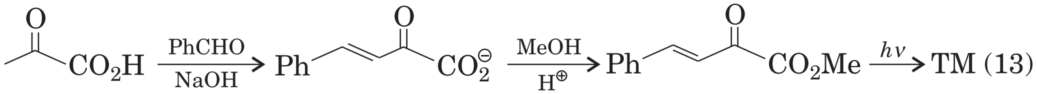
Synthesis



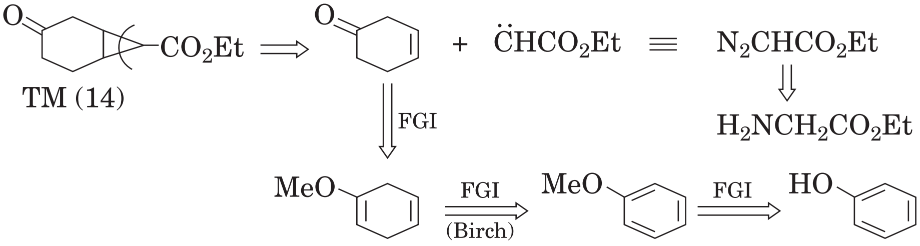
(d) *Retrosynthetic analysis*



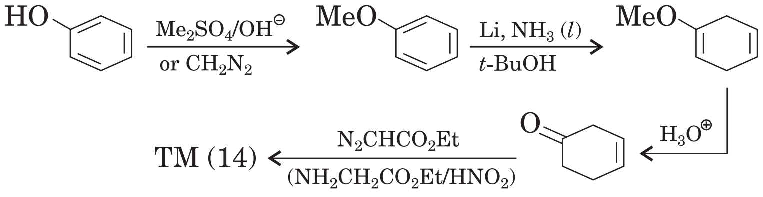
Synthesis



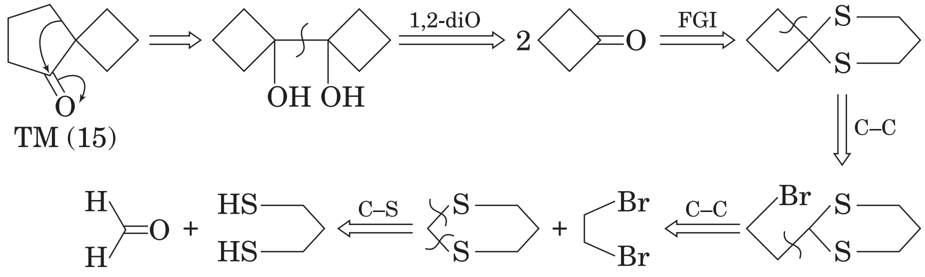
(e) *Retrosynthetic analysis*



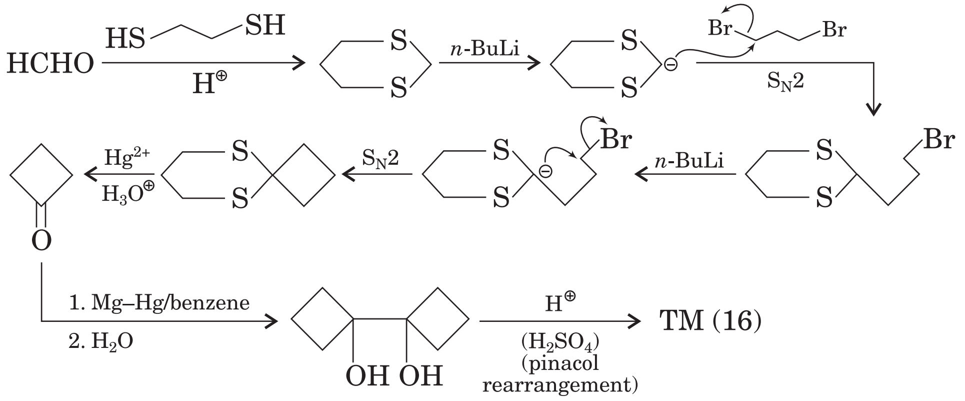
Synthesis



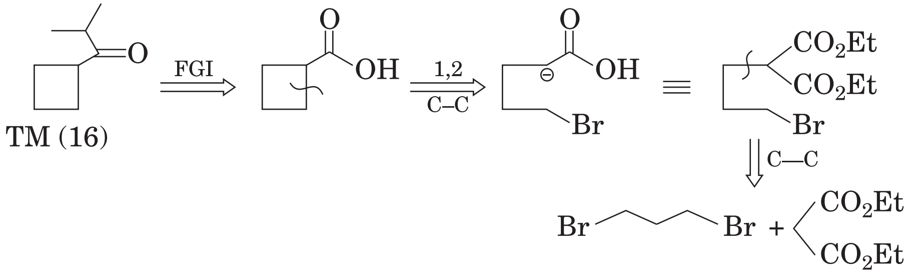
(f) *Retrosynthetic analysis*



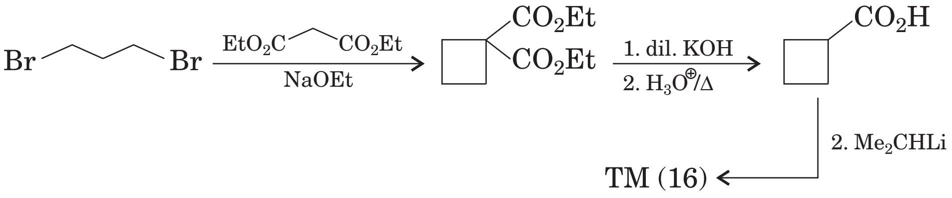
Synthesis



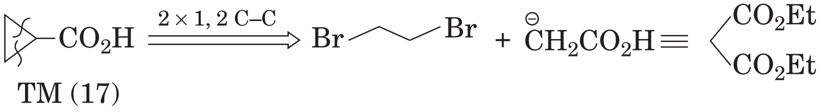
(g) *Retrosynthetic analysis*



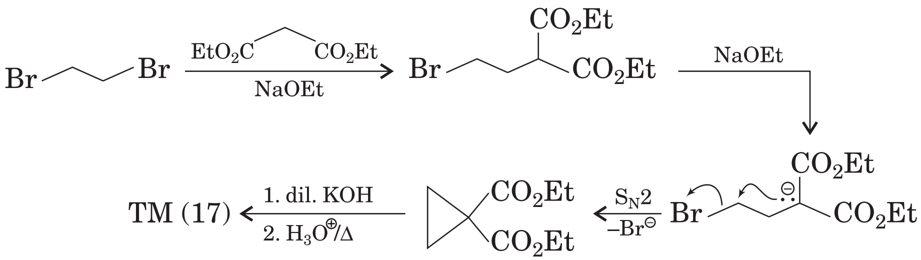
Synthesis



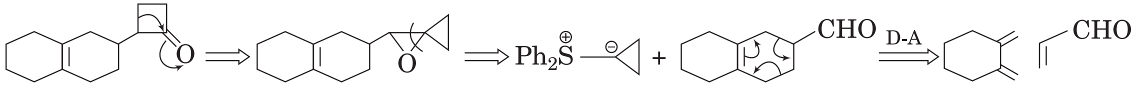
(h) *Retrosynthetic analysis*



Synthesis

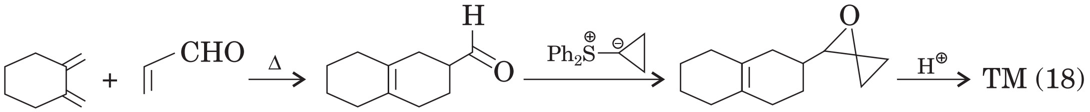


(i) *Retrosynthetic analysis*



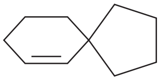
TM(18)

Synthesis



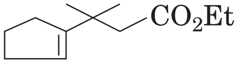
3. **A skeletal rearrangement is involved in each of the following target molecule. Outline their synthesis with proper retrosynthetic analysis.**

(a)



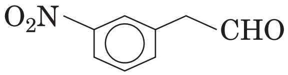
TM (19)

(b)



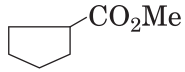
TM (20)

(c)



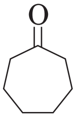
TM (21)

(d)



TM (22)

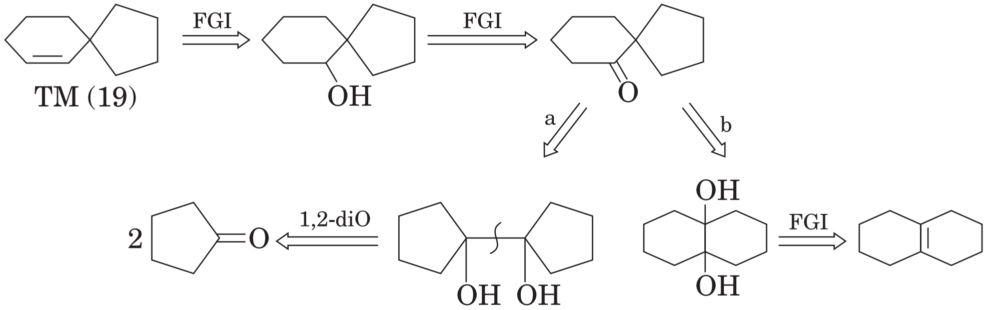
(e)



TM (23)

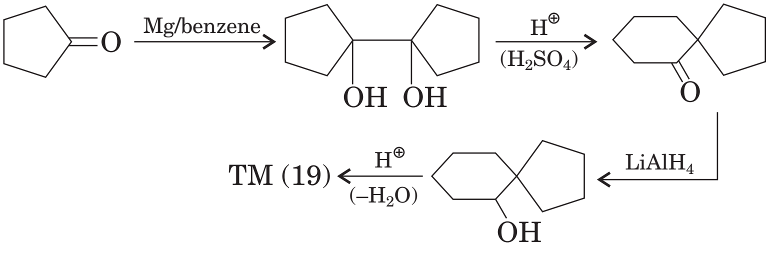
Solution

(a) *Retrosynthetic analysis*

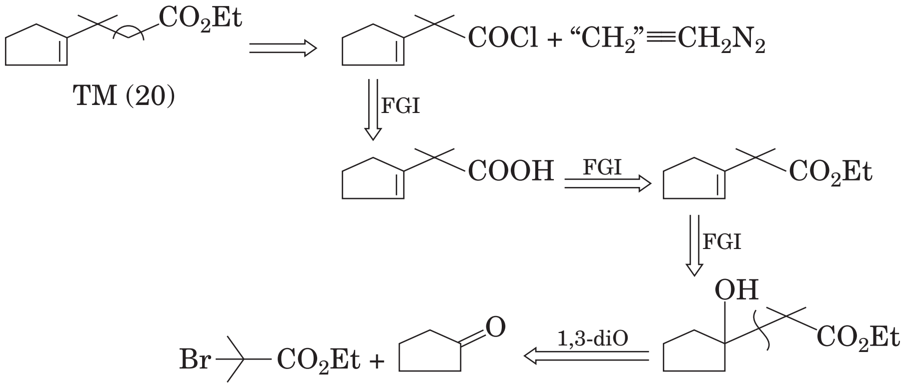


The pinacol rearrangement is a useful approach to *t*-alkyl ketones which are otherwise difficult to prepare. Two symmetrical pinacols are generated when the rearrangement is drawn in reverse (a and b).

Synthesis

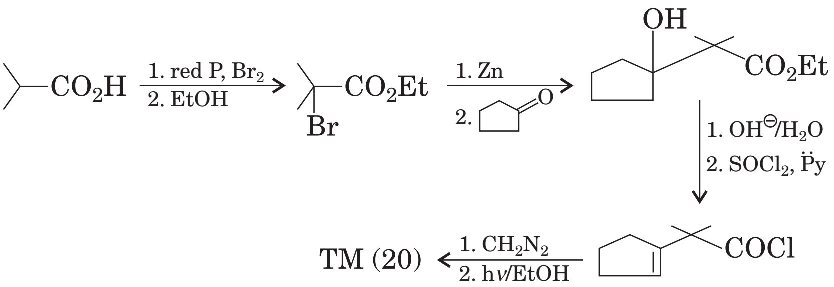


(b) *Retrosynthetic analysis*

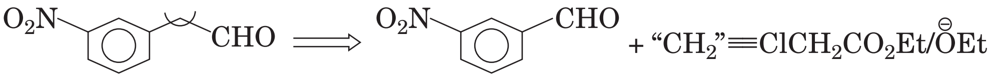


The disconnection involves removal of carbene. This corresponds to the *Arndt-Esistert synthesis (Wolff rearrangement)*.

Synthesis



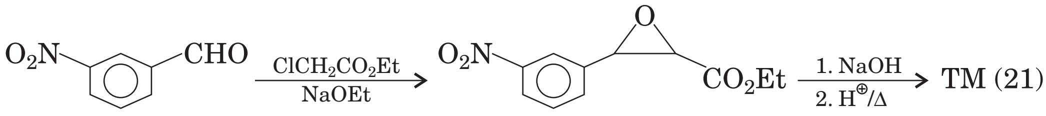
(c) *Retrosynthetic analysis*



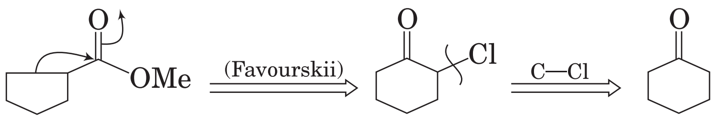
TM (21)

The Darzens reaction can be used successfully to synthesize the target molecule from the aromatic aldehyde. The disconnection is to remove carbene.

Synthesis



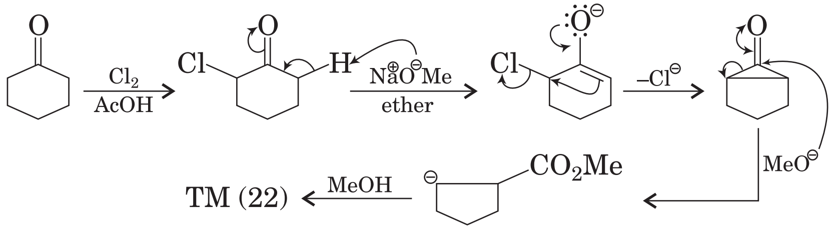
(d) *Retrosynthetic analysis*



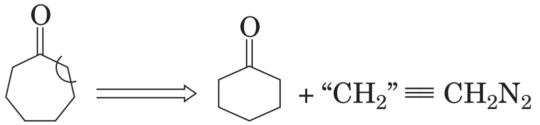
TM (22)

The disconnection is best seen when reverse the Favorskii rearrangement.

Synthesis



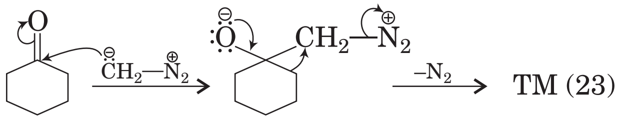
(e) *Retrosynthetic analysis*



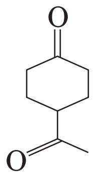
TM (23)

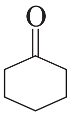
Diazomethane converts a ketone to its next higher homolog.

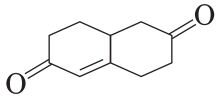
Synthesis

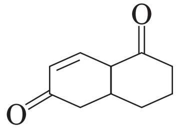

O
$\overset{\ominus}{C}H_2—\overset{\oplus}{N}_2$
:Ö:⊖
$CH_2—\overset{\oplus}{N}_2$
$-N_2$
TM (23)

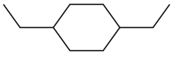
4. Using disconnection approach, design a convenient synthesis for each of the following target molecules:

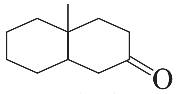
(a)

TM (24)

(b)

TM (25)

(c)

TM (26)

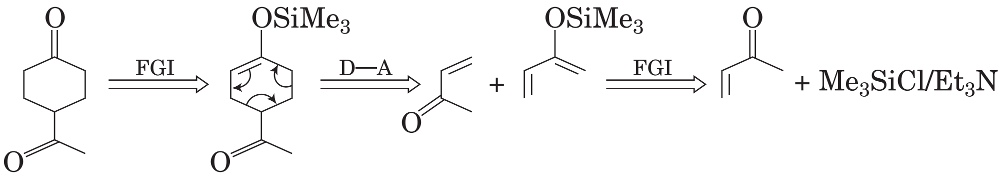
(d)

TM (27)

(e)

TM (28)

(f)

TM (29)

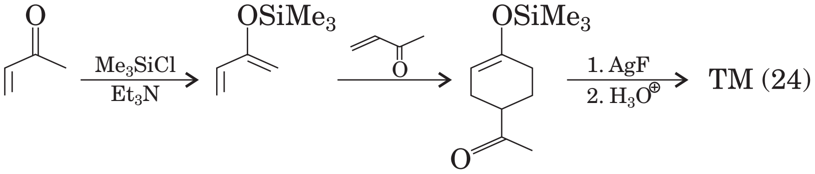
Solution

(a) *Retrosynthetic analysis*

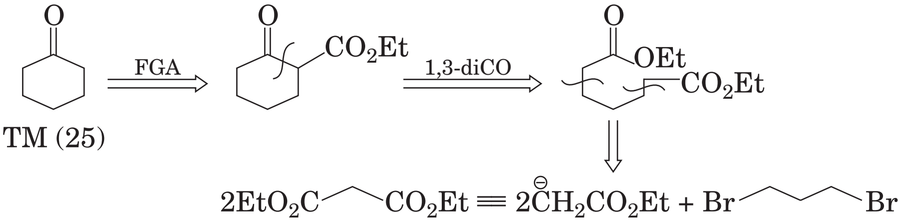


TM (24)

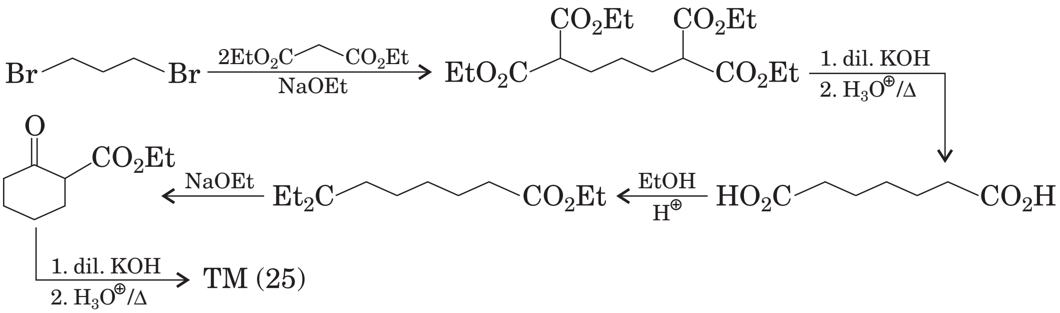
Synthesis



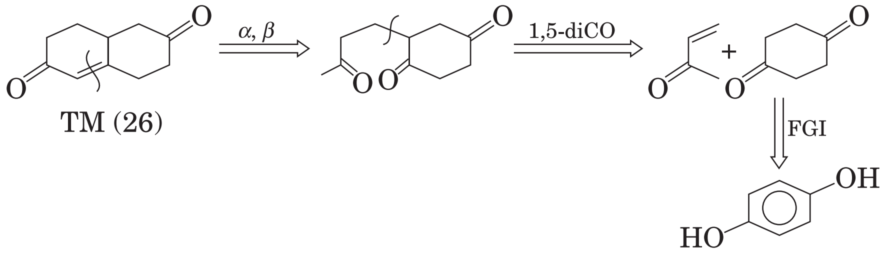
(b) *Retrosynthetic analysis*



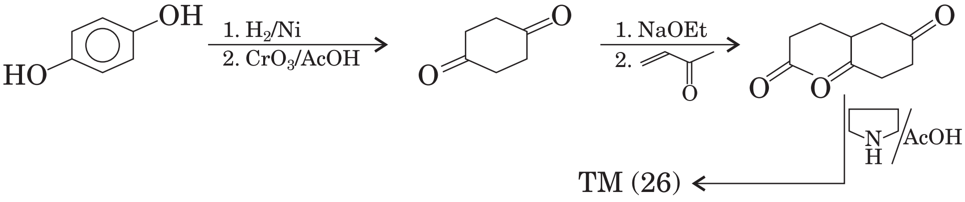
Synthesis



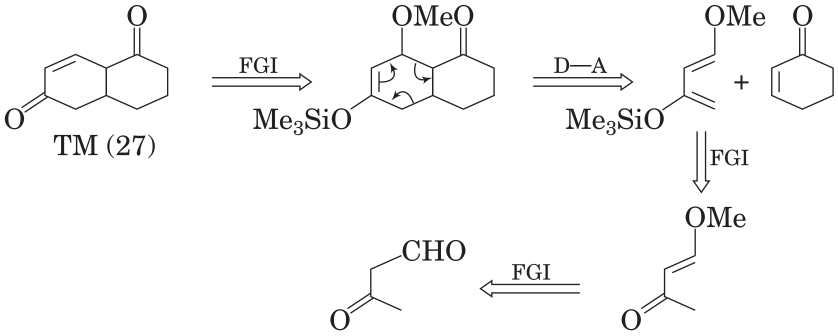
(c) *Retrosynthetic analysis*



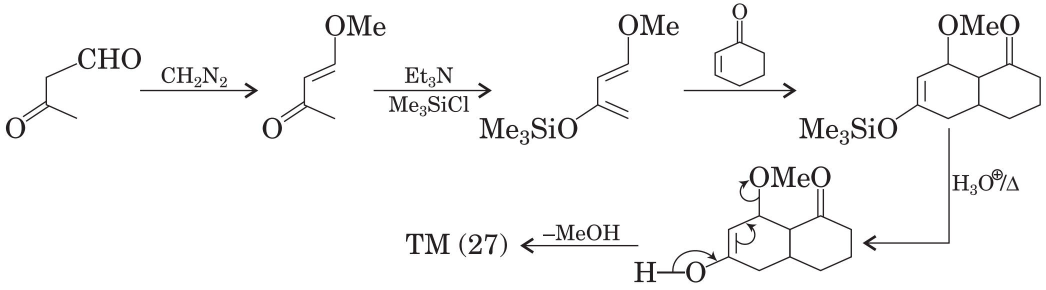
Synthesis



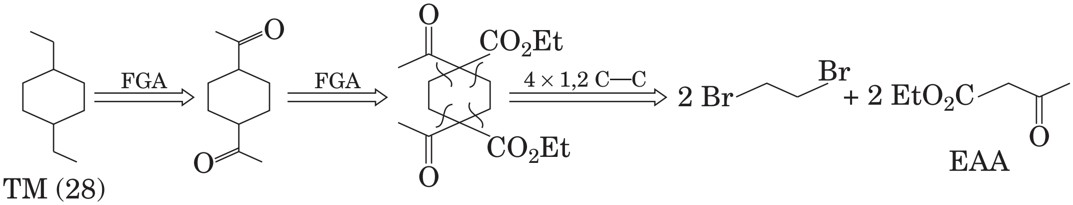
(d) *Retrosynthetic analysis*



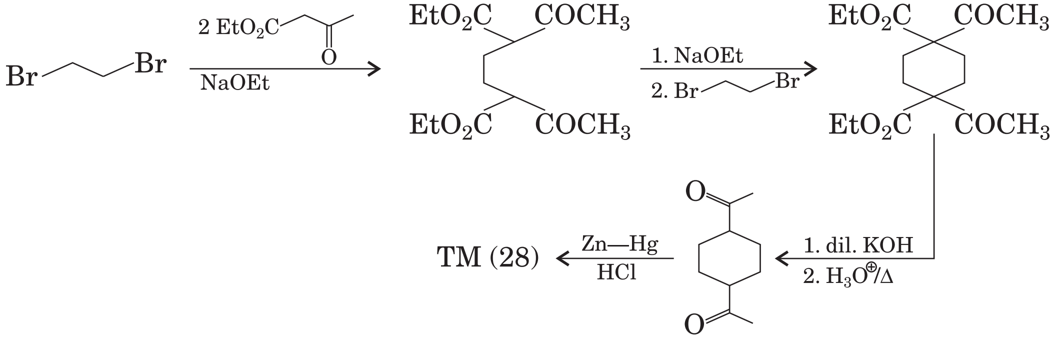
Synthesis



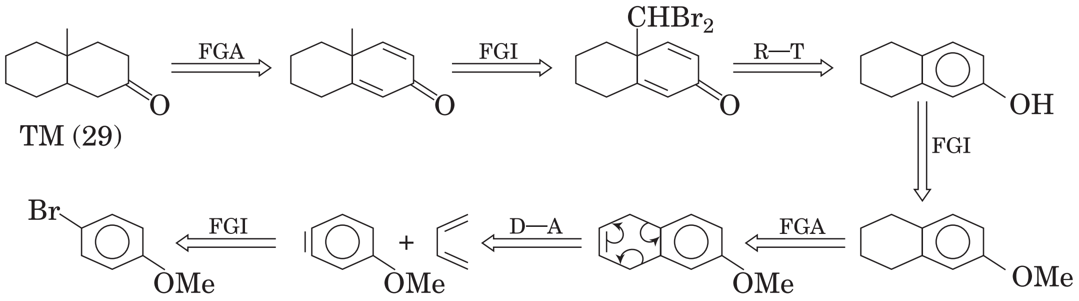
(e) *Retrosynthetic analysis*



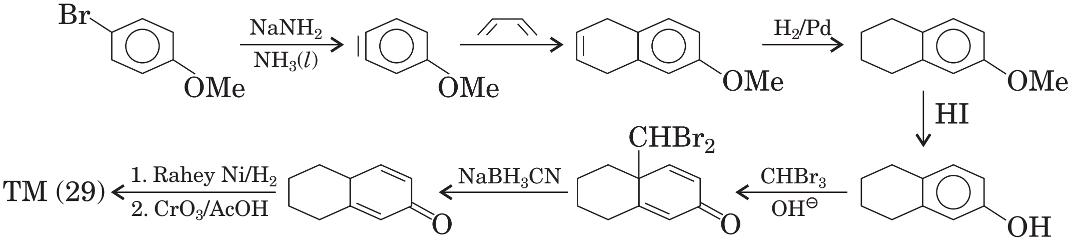
Synthesis



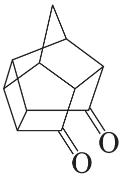
(f) *Retrosynthetic analysis*



Synthesis

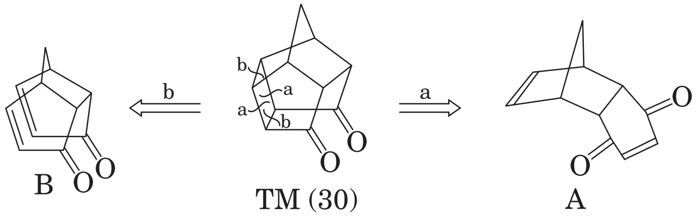


5. **Using disconnection approach, design a suitable synthesis of the following compound:**

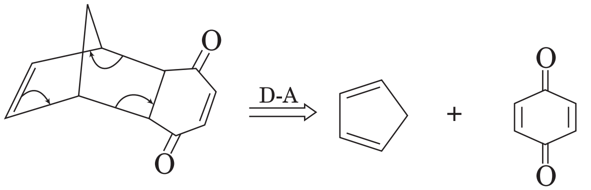


TM (30)

Solution This cage-like structure contains six-, five- and four-membered rings. We are interested with the four-membered rings and can disconnect this in two ways (a, b):

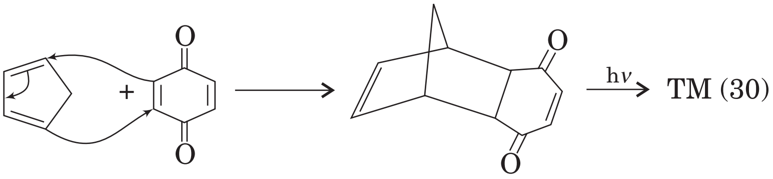


We could continue with B by disconnecting the α,β-unsaturated carbonyl groups, but the intermediate A is recognised as a Diels–Alder adduct, and this is, in fact, the shorter route. Also, both of these two starting materials are readily available.

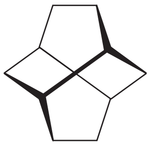


Adduct Diene Dienophile

Synthesis



6. Based on disconnection approach, give a convenient synthesis of the following hydrocarbon:

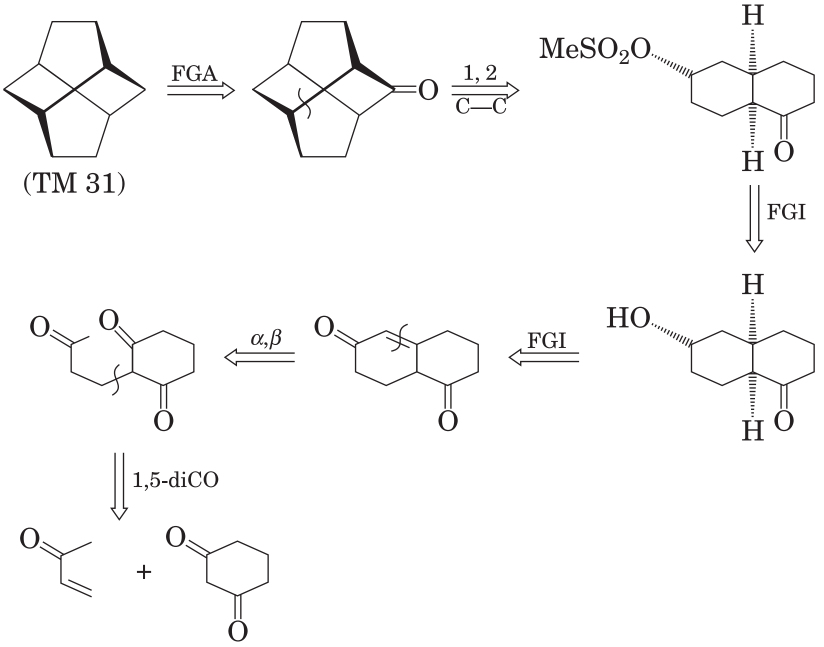


(TM 31)

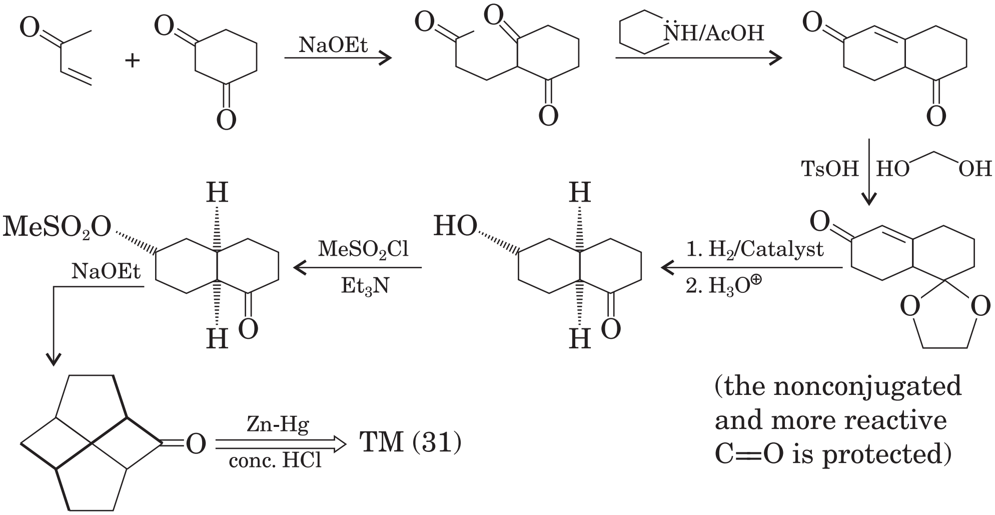
Twistane

Solution

Retrosynthetic analysis

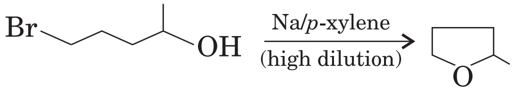


Synthesis

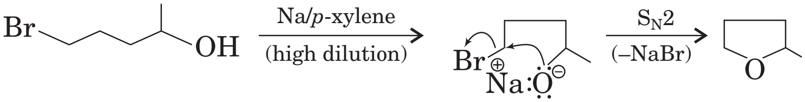


(the nonconjugated and more reactive C=O is protected)

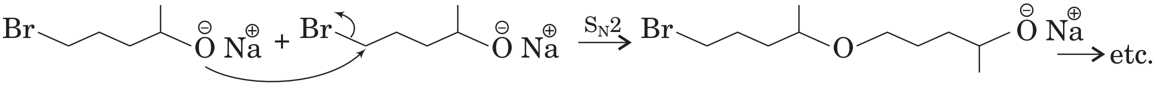
7. Give the mechanism of the following reaction leading to the formation of a cyclic ether and explain why it is carried out at higher dilution.



Solution The mechanism of the reaction is as follows:



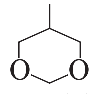
The reaction is carried out at high dilution because under such conditions the intermolecular distance becomes greater than the intramolecular reactive sites and as a result, cyclization occurs instead of polymerization (a likely result in concentrated solution) as shown below:



STUDY PROBLEMS

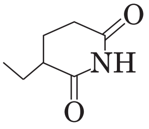
1. Outline the synthesis of each of the following target molecules with proper retrosynthetic analysis:

(a)



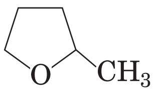
TM (1)

(b)

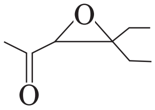


TM (2)

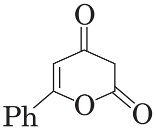
(c)



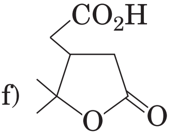
TM (3)

(d)


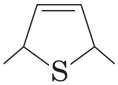
TM (4)

(e)


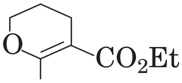
TM (5)

(f)


TM (6)

(g)


TM (7)

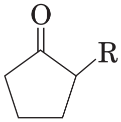
(h)


TM (8)

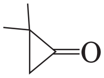
2. Based on disconnection approach, give a convenient synthesis of each of the following target molecules.

(a)

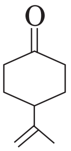
TM (9)

(b)


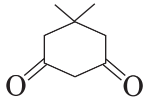
TM (10)

(c)


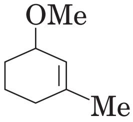
TM (11)

(d)


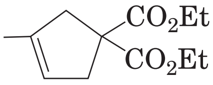
TM (12)

(e)


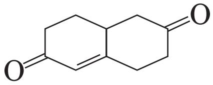
TM (13)

(f)


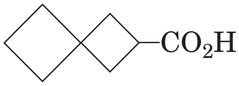
TM (14)

(g)


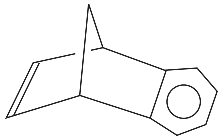
TM (15)

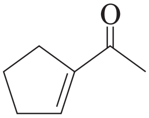
(h)


TM (16)

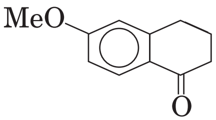
(i)


TM (17)

(j)

TM (18)

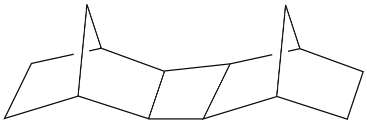
(k)


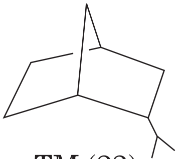
TM (19)

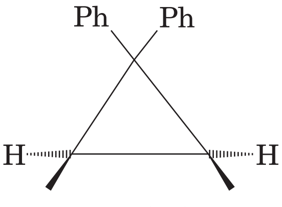
(l)


TM (20)

3. Give synthesis of each of the following compounds with proper retrosynthetic analysis:

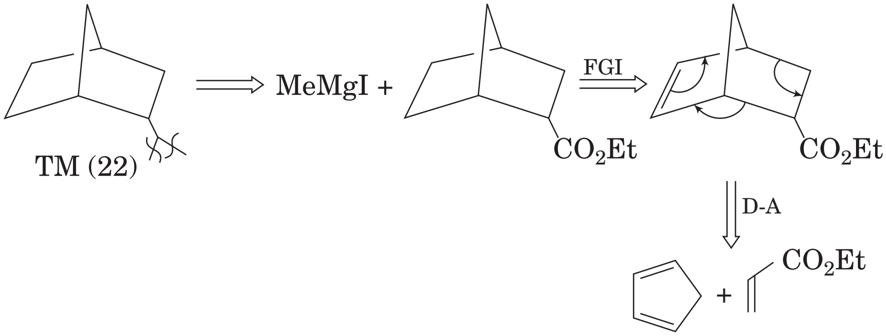
(a)

TM (21)

(b)

TM (22)

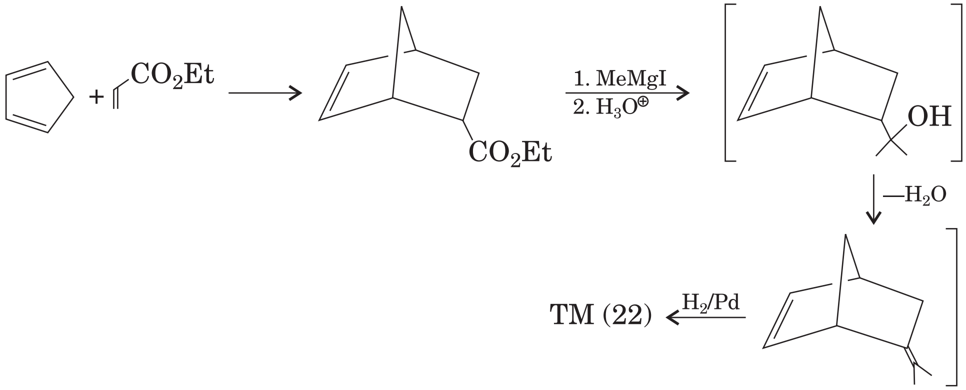
(c)


TM (23)

[**Hint:** (b)



Synthesis

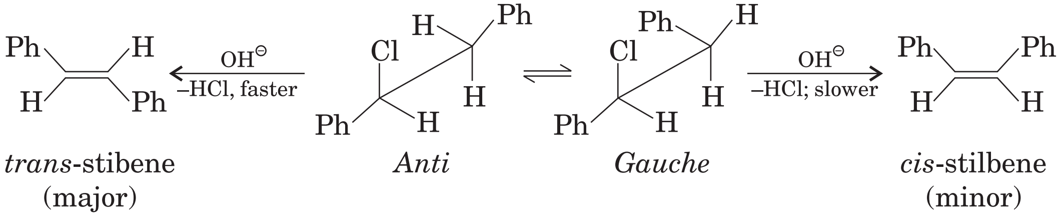


3.3 ASYMMETRIC SYNTHESIS

3.3.1 Stereoselective and Stereospecific Reactions

3.3.1.1 Stereoselective Reaction

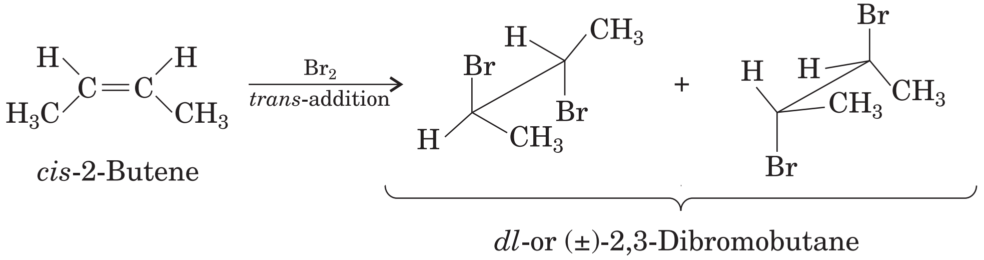
A reaction that yields predominantly one stereoisomer (or one pair of enantiomers) of several possible diastereoisomers is called a *stereoselective reaction*. For example, of the two isomeric stilbenes *trans*-stilbene is formed predominantly when 1,2-diphenyl-1-chloroethane undergoes dehydrochlorination in the presence of a base.

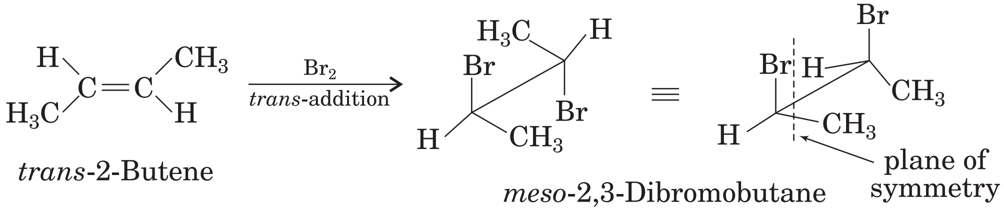


1,2-Diphenyl-1-chloroethane

3.3.1.2 Stereospecific Reaction

A stereospecific reaction is one in which the stereochemically different starting compounds lead to stereochemically different products. For example, *cis*-2-butene undergoes bromination to give only *dl*-2,3-dibromobutane while the *trans*-isomer undergoes bromination to give *meso*-2,3-dibromobutane. Since two diastereoisomeric 2-butenes give two different stereoisomeric products, the reaction is a stereospecific one.





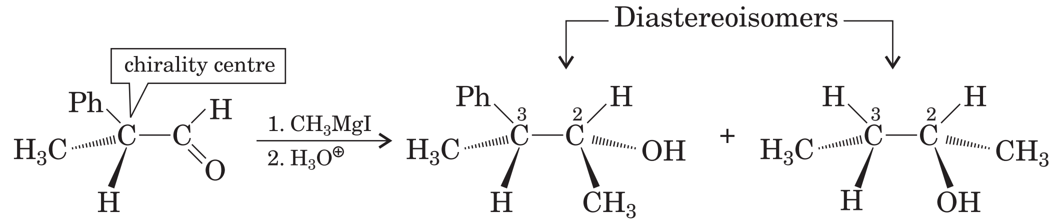
Based on these definitions of the terms stereospecificity and stereoselectivity, it may be concluded that all *stereospecific reactions are stereoselective (100%) but all stereoselective reactions are not necessarily stereospecific* and this is because there are stereoselective reactions in which the reactant cannot exist as stereoisomers due to absence of a carbon—carbon double bond or a chirality centre.

A stereoselective reaction is again classified as *diastereoselective* or *enantioselective* depending on whether the products are diastereoisomers or enantiomers.

3.3.2 Asymmetric Synthesis

Reactions in which an achiral and a chiral substrate produce enantiomeric and diastereomeric products respectively in unequal amounts are called *asymmetric synthesis*. In fact, asymmetric synthesis is a generalised name of stereoselective reactions and therefore, it comprises both enantioselective and diastereoselective reactions. An asymmetric synthesis requires the presence of some kind of chiral influence. Therefore, the presence of a chiral substrate, reagent, catalyst, solvent or physical force (such as circularly polarized light) is required for the preferential formation of one stereoisomer (either an enantiomer or a diasteroisomer). The term asymmetric induction is used to mean the control of selectivity exerted by the chiral influence. Two typical examples of asymmetric synthesis are given as follows.

1.



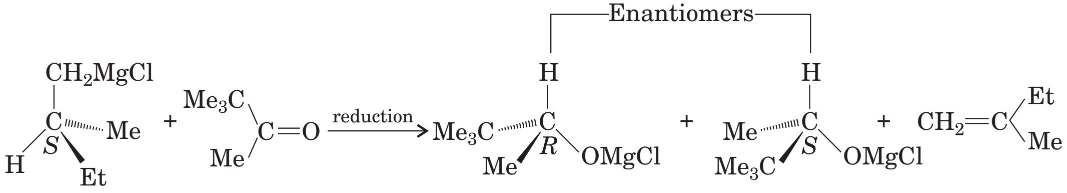
(*R*)-2-Phenylpropanal (chiral substrate)

(2*R*, 3*R*)-3-Phenyl-2-butanol (major)

(2*S*, 3*R*)-3-Phenyl-2-butanol (minor)

In this example, preferential attack on one of the diastereotopic faces of the chiral aldehyde occurs due to asymmetric induction (intramolecular) caused by the existing chirality centre. The reaction is called *diastereoselective* because it takes place through diastereoface differentiation.

2.



Chiral reagent

Prochiral substrate

(major product)

(minor product)

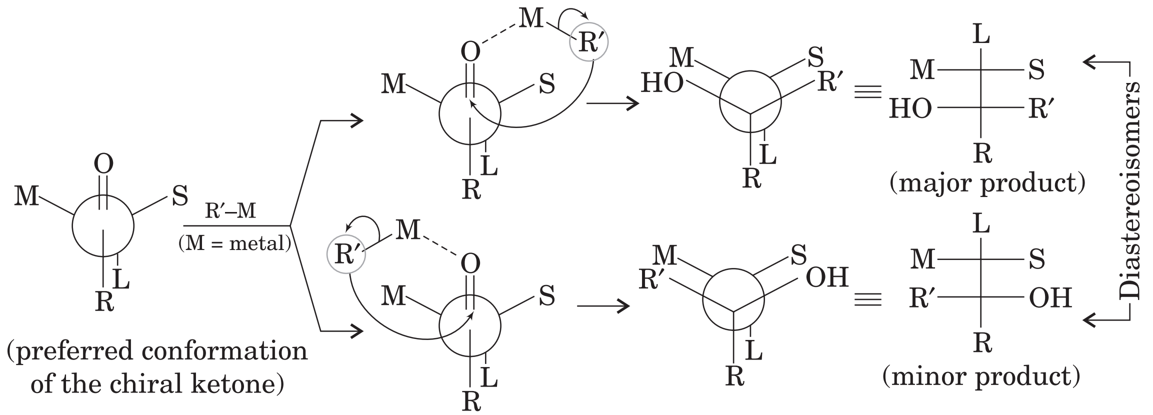
In this reaction, a new chiral centre is created on a prochiral centre by the preferred attack on one of the enantiotropic faces by a chiral reagent. The reaction occurs through enantioface differentiation and is called *enantioselective*. It is a case of intermolecular asymmetric induction.

In asymmetric synthesis, the chiral agent plays an active role and be integral to the transition state, so that two diasterioisomeric transition states are formed. Competing reactions with diastereoisomeric transition states have different activation energies ($\Delta G^\ddagger$). Because of this, one stereoisomer is produced more rapidly and in excess over the other.

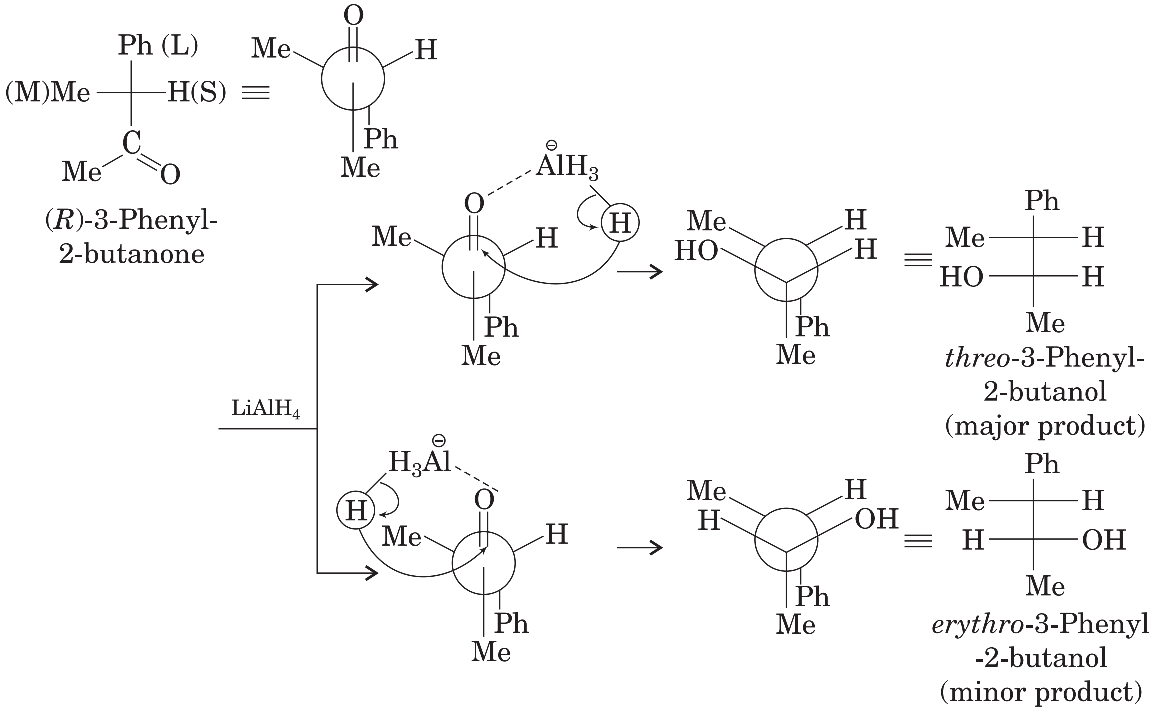
Cram's rule Cram's rule accounts for the preferential formation of one diastereoisomer in terms of steric interactions involved in the kinetically controlled addition reactions of chiral carbonyl compounds with organometallic and metal hydride reagents.

According to Cram's rule, nucleophilic attack on a carbonyl carbon of a chiral carbonyl compound like $RCO\overset{*}{C}LMS$, where L, M and S stand for large, medium and small groups, respectively, will take place from the less hindered side, i.e., from the side of the small group(s) in a conformation where the $>C=O$ group is flanked by the two smaller groups (M and S) with the large group (L) remaining eclipsed with R (the *open chain* model). The

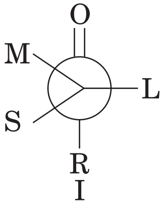
$\rangle C{=}O$ group gets complexed with the metal atom of the reagent and in fact, becomes effectively the bulkiest group and therefore, it is better to be placed between the two smaller groups. A typical Cram's model is shown below as its Newman projection.



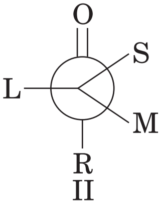
Lithium aluminium hydride ($LiAlH_4$) reduction of (R)-3-phenyl-2-butanone, for example, gives *threo*-3-phenylbutan-2-ol as the major product (70%). This observation could be well rationalised by applying Cram's rule. The hydride ion ($H^{\ominus}$) from $LiAlH_4$ attacks the carbonyl carbon atom from the less hindered side, i.e., from the side of hydrogen (the smaller substituent) to give the major product.



Felkin–Anh model According to the Felkin–Anh model, the lowest energy transition state corresponds to a conformation of the carbonyl compound in which the C—L bond (L = Large) is perpendicular to the >C=O group. The attacking nucleophile approaches the carbonyl carbon in a plane perpendicular to the >C=O part, from the side farthest from the C—L bond, maintaining an obtuse angle with >C=O, corresponding to approximately tetrahedral angle of Nu—C—O in the product. Two such conformations may be drawn using Newman projection formula.

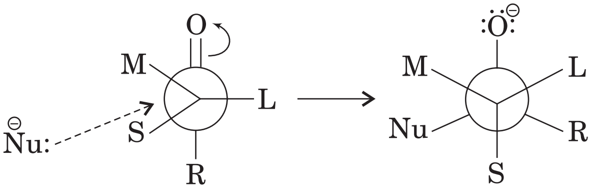


I

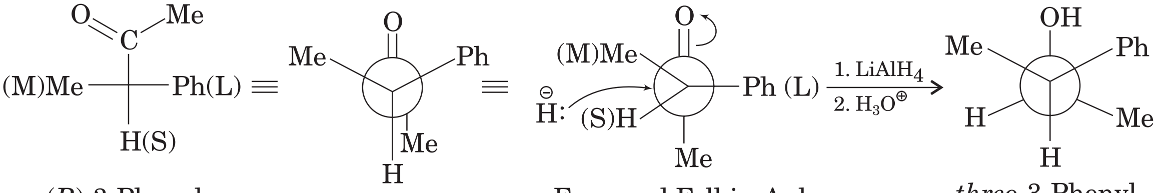


II

In model I, the R group is flanked by the small group S and the large group L while in model II, the R group is flanked by the medium group M and the large group L. From steric point of view the model I is, therefore, more preferred than the model II. So, the reaction takes place through the conformation I. According to the model I, the formation of the major product (diastereoisomer) can be shown as follows:



Reduction of (R)-PhCHMeCOMe by $LiAlH_4$, for example, takes place by following the Felkin-Anh model to give *threo*-3-phenyl-2-butanol as the major product.

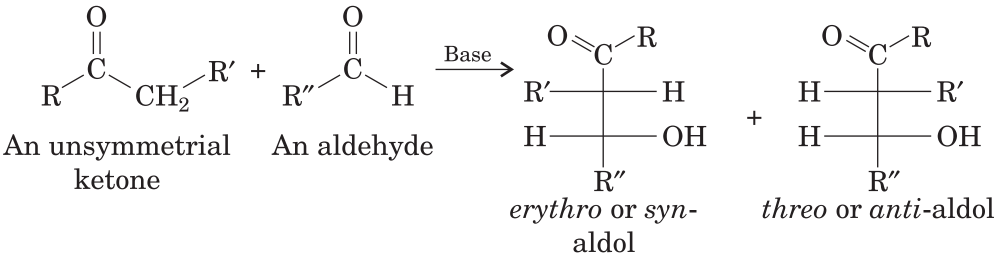


(R)-3-Phenyl-2-butanone

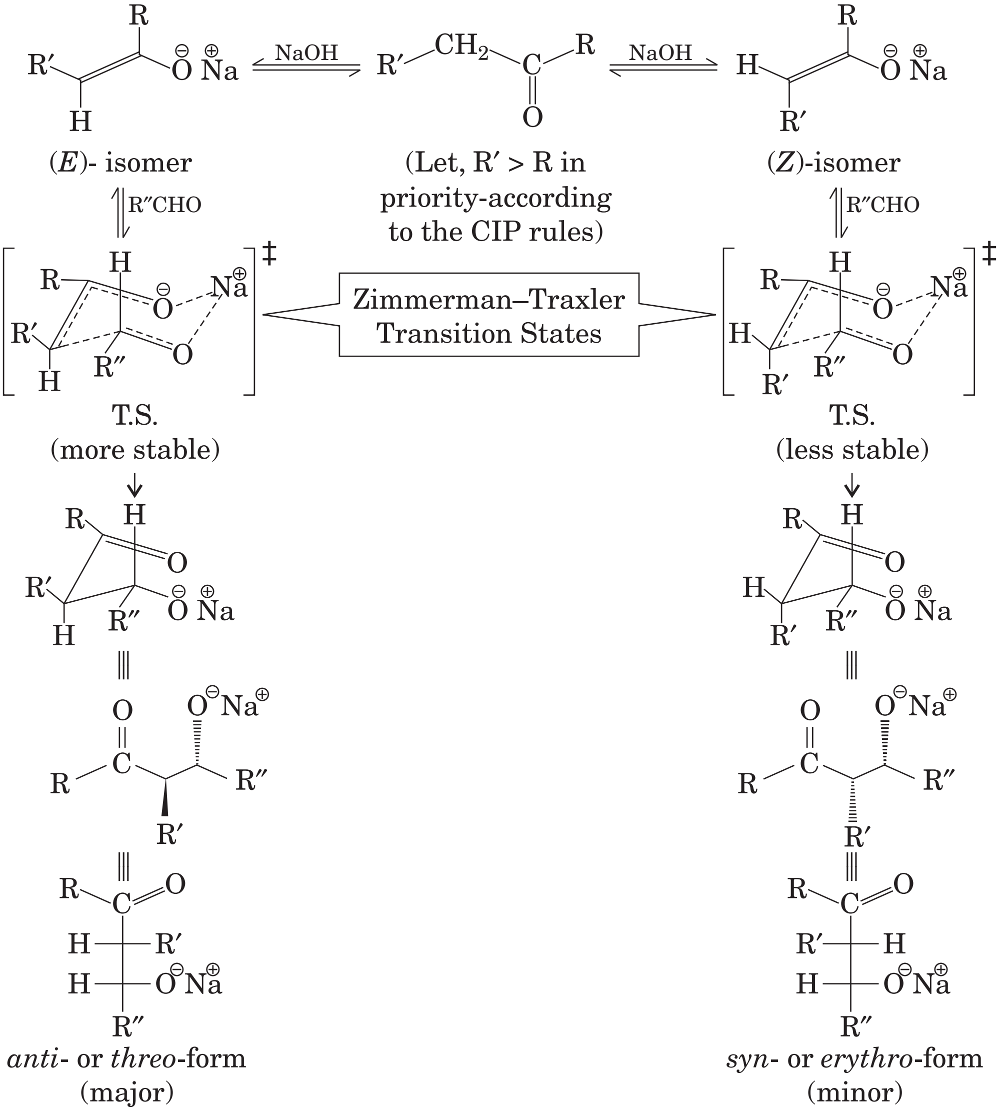
Favoured Felkin-Anh model

threo-3-Phenyl-2-butanol (major product)

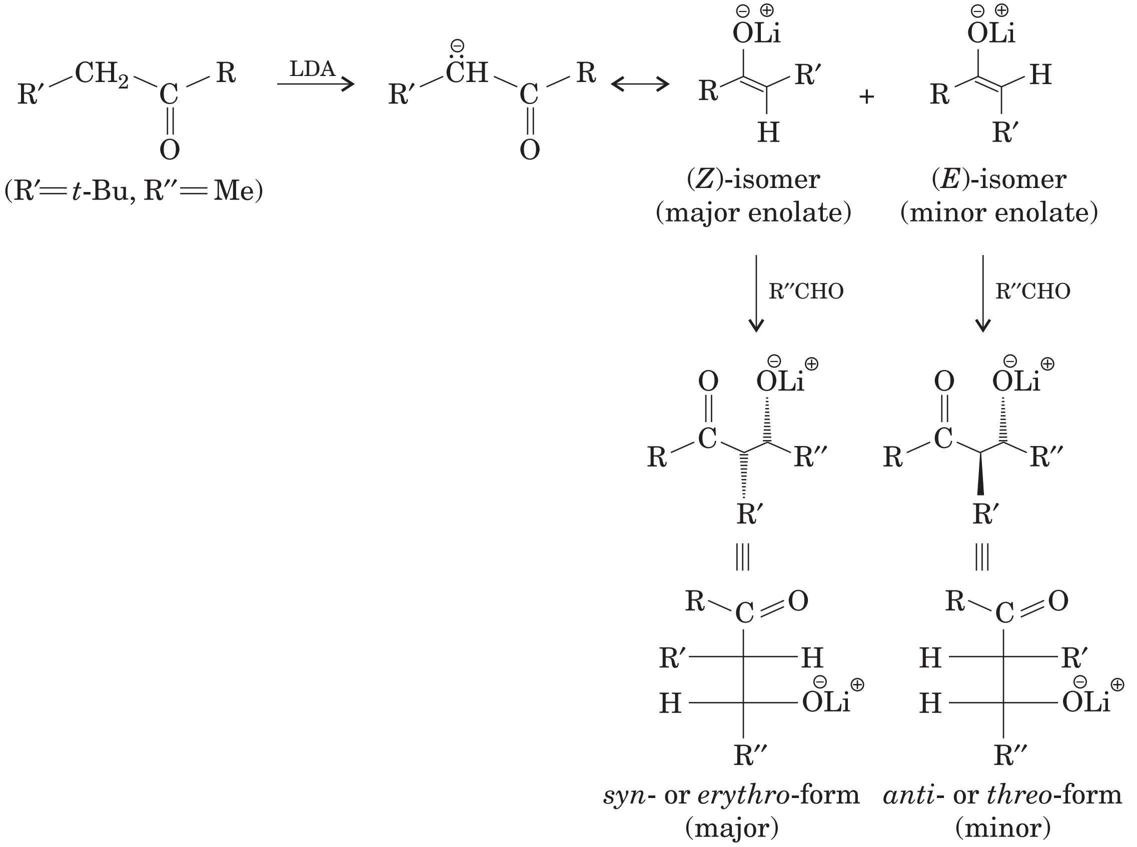
Zimmermann–Traxler model: Stereochemical aspect of aldol addition When two molecules of the same achiral aldehydes are involved in aldol addition reaction, a single chirality centre is created and the reaction leads to the formation of enantiomeric aldols (racemic mixture). However, when an unsymmetrical achiral ketone reacts with an achiral aldehyde, two chiral centres are generated in the product and as a result, two diastereoisomeric aldols (*threo* or *anti* and *erythro* or *syn*) are formed.



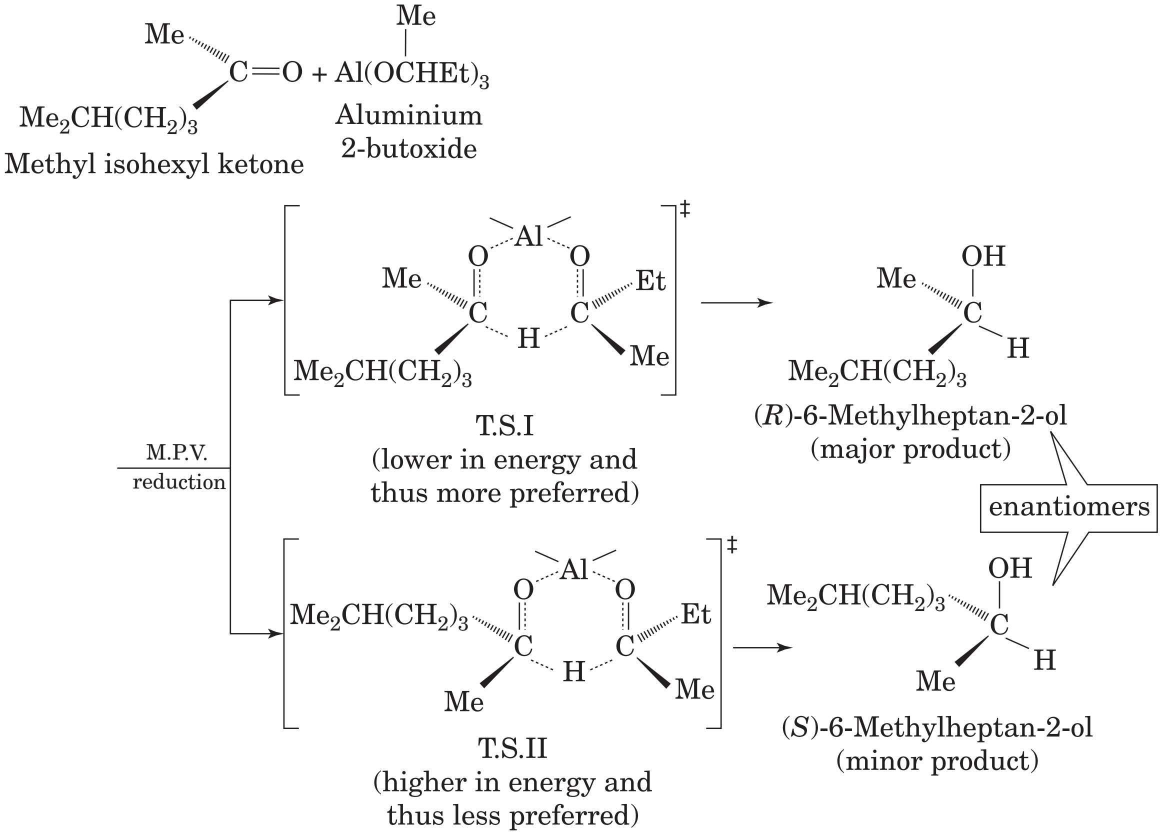
Under thermodynamic conditions involving a weaker base (e.g., $OH^{\ominus}$), high temperature and long reaction time, the (*Z*)- or (*E*)-forms of enolate remains in rapid equilibrium and in such a case the diastereoselectivity is controlled by the relative stability of the cyclic chair-like transition states. This is what is called the *Zimmerman–Traxler* transition state. Only one enantiomer of each product is shown in the following sequence of reactions.


NaOH
NaOH
(*E*)- isomer
(Let, R′ > R in priority-according to the CIP rules)
(*Z*)-isomer
R″CHO
R″CHO
Zimmerman–Traxler Transition States
T.S. (more stable)
T.S. (less stable)
anti- or *threo*-form (major)
syn- or *erythro*-form (minor)

The chair-like transition state (including the metal ion as a member of the six-membered ring) leading to the formation of the threo- or *anti*-aldol has both R′ and R″ in approximately equatorial positions, whereas in that leading to the *erythro*- or *syn*-aldol R′ assumes the less stable axial position. Since the T.S. leading to the *anti*-aldol possesses lower energy, it will be formed at a faster rate and as a consequence, it predominates in the product mixture. This type of diastereoselectivity is due to thermodynamic control. The reaction can also be made to proceed through kinetic control by using very strong base like LDA, low temperature, and short reaction time. Under such conditions, (Z)-enolate is formed rapidly (almost irreversibly) and predominantly to give the *syn*-aldol as the major product. The *syn*-product is the kinetic product. Hence, in this case, the relative amount of the diastereoisomeric enolate determines the product composition. This type of diastereoselectivity depends on the size of the R′ group. *Syn-anti* ratio is almost 9.8:1 when R′ = *t*-Bu and R = Me but when R′ is isopropyl group the *syn-anti* ratio is 4:1.



Enantioselectivity: Kinetically controlled M.P.V reduction When methyl isohexyl ketone is allowed to react with aluminium 2-butoxide in 2-butanol, (*R*)-6-methylheptan-2-ol is obtained as the major product. The reaction is, therefore, enantioselective.

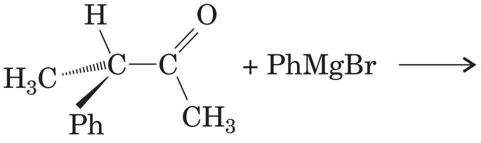


The reaction proceeds through the low-energy transition state I in which the larger groups (–Et and –$CH_2CH_2CH_2CHMe_2$) are placed on opposite sides of the plane of six-membered ring and as a result (*R*)-6-methylheptan-2-ol is obtained as the major product.

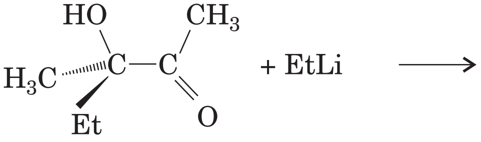
SOLVED PROBLEMS

1. **Use Cram's rule to predict the major product in each of the following diastereoselective reactions:**

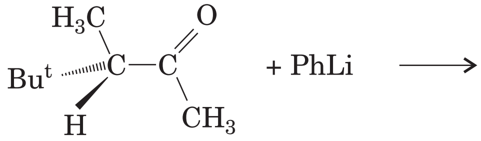
(a)



(b)

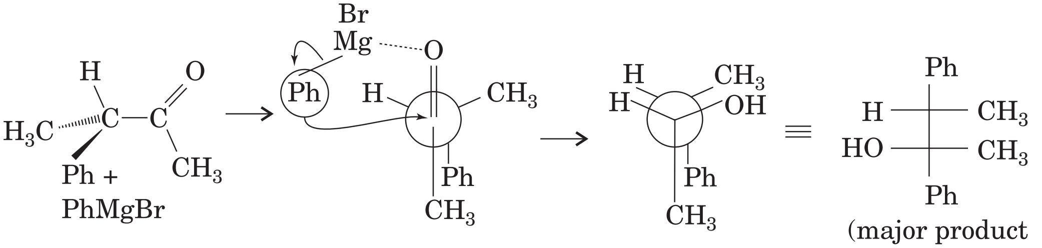


(c)



Solution

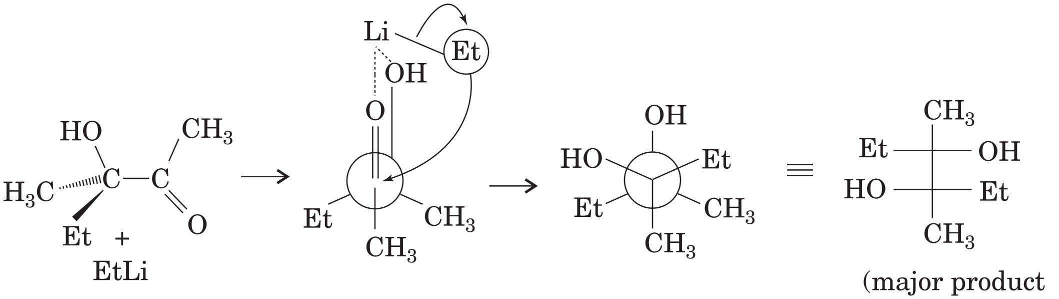
(a)



(major product according to Cram's open chain model)

Nucleophilic attack by Ph$^\ominus$ on the carbonyl carbon atom occurs from the less crowded side (from the side of the small substituent) to yield the major product.

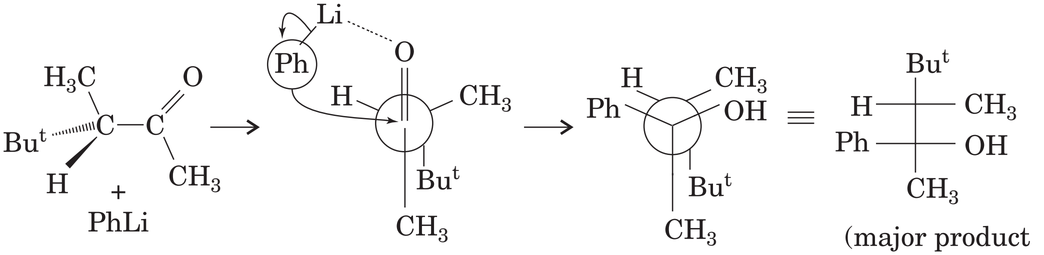
(b)



(major product according to rigid cycle model)

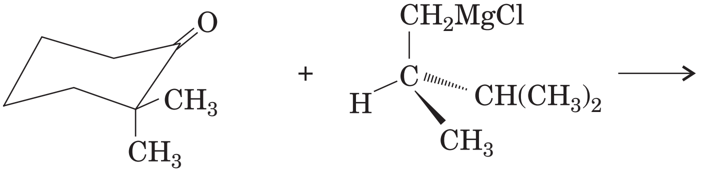
This observation can be explained on the basis of a regid *cyclic model* in which the metallic part of the reagent is doubly co-ordinated to form a five-membered ring. Since the complexing group is medium (M), the nucleophile attacks the carbonyl carbon from the side of the small group (S) and the cyclic model predicts the same stereochemistry as the open chain model.

(c)



(major product according to Cram's open chain model)

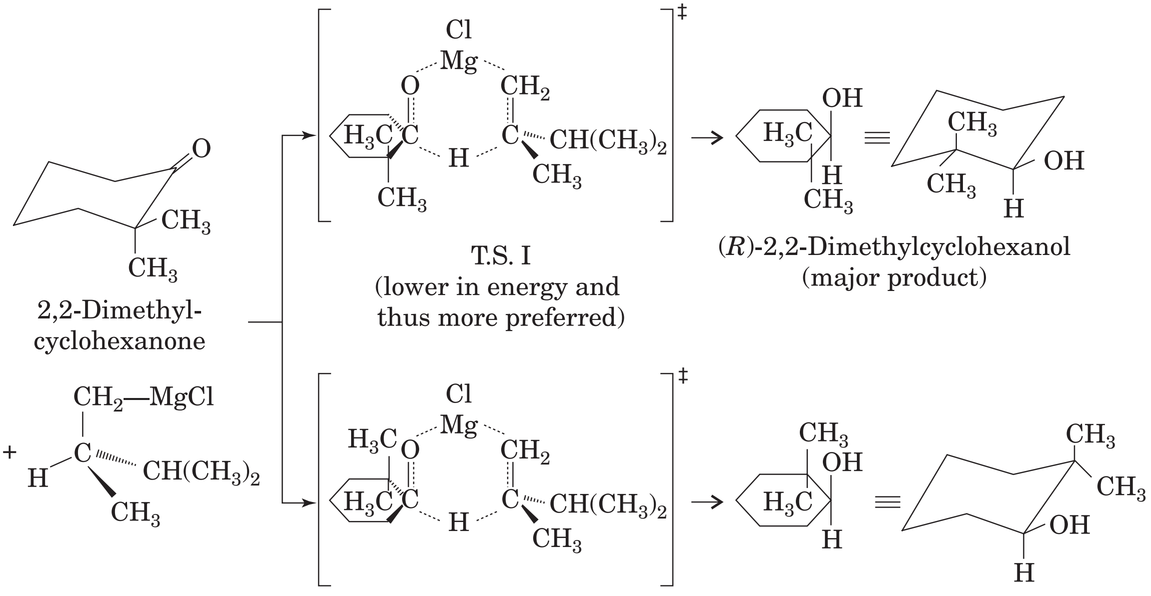
2. Predict the major product expected to be obtained when 2,2-dimethylcyclohexanone is reduced by the given chiral Grignard reagent:



2,2-Dimethylcyclohexanone

A chiral Grignard reagent

Solution Because of severe steric hindrance, the normal Grignard reaction to form a 3° alcohol does not take place and instead of that, reduction occurs to form (R)-2,2-dimethylcyclohexanol as the major product (an enantioselective reaction).



2,2-Dimethyl-cyclohexanone

T.S. I (lower in energy and thus more preferred)

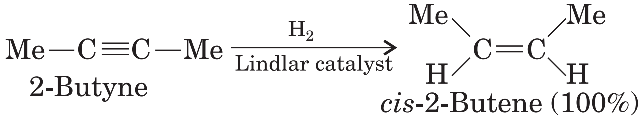
(*R*)-2,2-Dimethylcyclohexanol (major product)

T.S. II (higher in energy and thus less preferred)

(*S*)-2,2-Dimethylcyclohexanol (minor product)

3. Explain why the following reactions are not stereospecific:

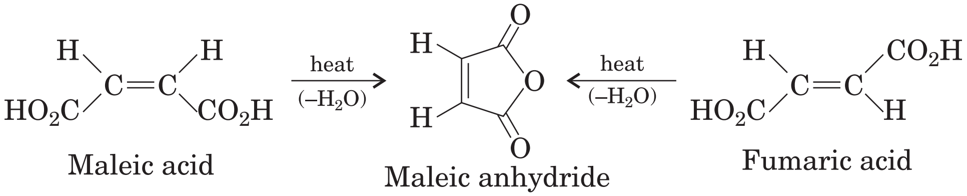
(a)



2-Butyne

cis-2-Butene (100%)

(b)



Solution

(a) The reaction is not stereospecific because the substrate cannot exist as stereoisomers.

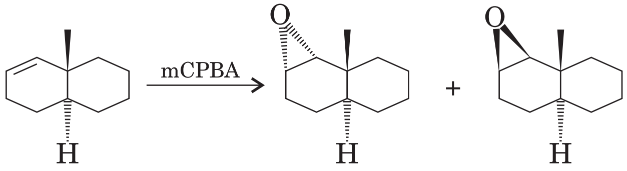
(b) The reaction is not stereospecific because two different stereoisomeric substrates do not lead to two different stereoisomeric products.

STUDY PROBLEMS

1. Which of the following reactions are stereospecific and why?

   S_N1, S_N2, E1, E2

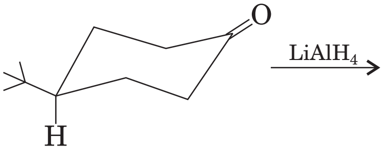
2. Give examples of (i) intermolecular asymmetric induction and (ii) intramolecular asymmetric induction.
3. Explain the principle of asymmetric synthesis.
4. Explain the stereoselectivity of the following reaction:



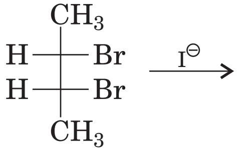
I II (major) III (minor)

5. All stereospecific reactions are stereoselective, but all stereoselective reactions are not necessarily stereospecific – explain.
6. Identify the stereoselective and stereospecific reactions and give your reasoning:

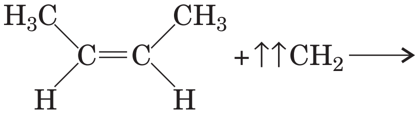
(a)



(b)



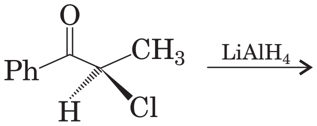
(c)



(d) $\mathrm{PhCHO + EtMgBr \xrightarrow[\text{(optically active solvent)}]{(+)-2,3\text{-Dimethoxybutane}}}$

(e) $\mathrm{PhCH{=}CHCHO + HCN \xrightarrow[\text{(optically active catalyst)}]{\text{Quinoline}}}$

7. Predict the major product in the following reaction based on Felkin–Anh model. Is it the observed product in the reaction? If not, predict the observed product and explain its formation.



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Organic Spectroscopy

4

Chapter Outline

Introduction

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- 4.1.2 Some Important Terms and Their Units
- 4.1.3 Electromagnetic Spectrum

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- 4.2.7 Types of Absorption Bands in UV Spectroscopy
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4.3 Infrared Spectroscopy

- 4.3.1 Basic Principle of IR Spectroscopy
- 4.3.2 IR Spectrum
- 4.3.3 Factors that Determine IR Absorption Position
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- 4.3.5 Functional Group Infrared Absorptions and Environmental Effects on Them
- 4.3.6 Infrared Correlation Table

INTRODUCTION

The study of organic compounds requires the knowledge of their molecular structures. The determination of the structure of an organic compound is, therefore, an essential task for an organic chemist. The classical methods applied for structure determination are not only unwieldy, laborious and time-consuming but also require a large quantity of the compound. Nowadays, various types of instrumental analysis of a minute amount of an organic compound by physical methods most often give necessary and sufficient information to establish its molecular structure undoubtedly. Molecular spectroscopy is probably the most important amongst them. Spectroscopy deals with the transitions induced in a chemical species by its interaction with photons of electromagnetic radiation. Spectroscopic methods are generally used to measure the energy difference between various molecular energy levels and to determine the molecular structures.

4.1 ENERGY AND THE ELECTROMAGNETIC SPECTRUM

4.1.1 Electromagnetic Radiation

Electromagnetic radiation is a form of energy that propagates as a wave through space at a characteristic velocity (the velocity of light). Each of the waves is composed of a magnetic component and an electric component oscillating in mutually perpendicular planes and the waves propagate at the same velocity through space (vacuum or material medium) in a direction perpendicular to the planes of the fields. Visible light is one type of electromagnetic radiation. Other common forms of electromagnetic radiation are X-rays, ultraviolet radiation (UV), infrared radiation (IR), microwaves, and radiofrequency waves (rf).

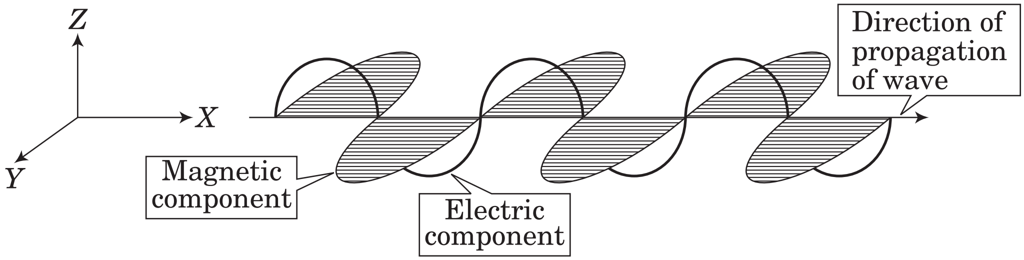


Figure 4.1 Propagation of the wave of electromagnetic radiation

According to quantum mechanics, the electromagnetic radiation has the properties of both a wave and a particle. That is, it has a duel nature: in some experiments it obeys wave theory and in others acts as a steam of massless particles called quanta (plural form of quantum) or photons. However, they are not seen together in the same experiment. Electromagnetic radiation is emitted, transmitted, and absorbed only in whole number of photons. Hence, it is quantized and thus, photon is also called quantum. The wave theory most concerns us here, and since the propagation of light waves involves both electric and magnetic forces, their common class name is *electromagnetic radiation* (Figure 4.1).

The velocity of the electromagnetic radiation in vacuum, is 2.998×10^8 ms^{-1} (denoted by c, the velocity of light). In a material medium, its velocity is given by $2.998 \times 10^8/n$ ms^{-1}, where n is the refractive index of the medium. A diagram of a wave, indicating the wavelength (λ), cycle and amplitude (A) may be given as follows (Figure 4.2).

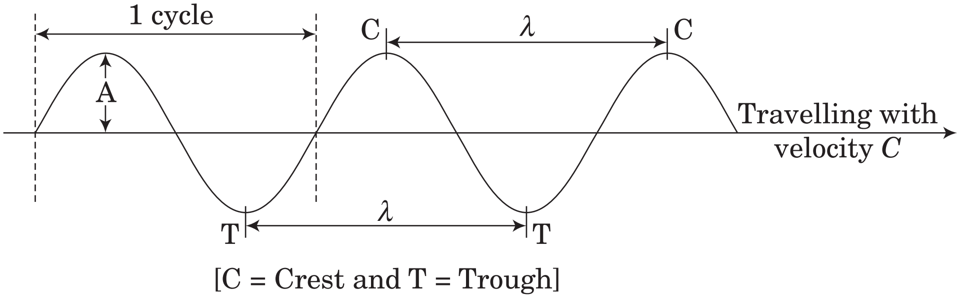


Figure 4.2 A diagram of a wave

4.1.2 Some Important Terms and Their Units

1. Wavelength (λ) It is the distance between consecutive crests or troughs in a particular wave. The wavelength of electromagnetic radiation is expressed in either metres (m), millimeters (1 mm = 10^{-3} m), micrometers (1 µm = 10^{6} m) or nanometers (1 nm = 10^{-9} m). [An older term for micrometre is *micron* (μ) and an older term for nanometre is millimicron (mµ).] It is also expressed in Angstrom units (1 Å = 10^{-8} cm).

2. Period (T) It is the time required to complete one full cycle. Its unit is *s*/cycle.

3. Frequency (ν) It is the number of full cycles of the wave that pass a given point in one second as the wave moves through space. It is expressed in cycle per second (s^{-1}) or in hertz (Hz), where 1 s^{-1} = 1 Hz.

4. Wavenumber ($\bar{\nu}$) It is the number of waves per centimetre and is expressed in reciprocal centimetre (cm^{-1}). It is a way of often expressing frequency in infrared spectroscopy.

The following are the relationships among the four quantities wavelength, wavenumber, frequency and velocity:

Quantity	Relationship	Units
Wavelength (λ)	$\lambda = \frac{1}{\bar{\nu}} = \frac{c}{\nu}$	m, µm, nm
Wavenumber ($\bar{\nu}$)	$\bar{\nu} = \frac{1}{\lambda} = \frac{\nu}{c}$	m^{-1}, cm^{-1}
Frequency (ν)	$\nu = \frac{c}{\lambda} = c\bar{\nu}$	s^{-1} (Hz)
Velocity (c)	$c = \nu\lambda = \frac{\nu}{\bar{\nu}}$	m s^{-1}

Relationship between Frequency (ν) and Energy (E) of a Wave Frequency and energy of a wave are related by the equation $E = h\nu$, where h = Planck's constant, 6.63×10^{-34} Js. Thus, the greater the frequency, the higher is the energy of the radiation.

Relationship between the Wavelength (λ) and Energy (E) of a Wave The wavelength and energy of a wave are related by the equation $E = hc/\lambda$. Thus, the longer the wavelength, the smaller is the energy.

That the energy associated with a radiation having wavelength 4,000 Å is 299.5 kJ mol^{-1} may be shown as follows:

$$\lambda = 4{,}000\ \text{Å} = 4{,}000 \times 10^{-8}\ \text{cm}$$

$$\begin{aligned}
E = hc/\lambda &= \frac{6.626 \times 10^{-27}\ \text{erg. sec} \times 2.998 \times 10^{10}\ \text{cm s}^{-1}}{4{,}000 \times 10^{-8}\ \text{cm}} \\
&= 4.968 \times 10^{-12}\ \text{erg} \\
&= \frac{4.968 \times 10^{-12} \times 6.023 \times 10^{23}}{4.18 \times 10^{10}}\ \text{kcal mol}^{-1} \\
&= 71.6\ \text{kcal mol}^{-1} \\
&= 71.6 \times 4.134\ \text{kJ mol}^{-1} = 299.5\ \text{kJ mol}^{-1}
\end{aligned}$$

[A convenient formula that relates wavelength (in nm) to the energy of electromagnetic radiation is the following:

$$E(\text{in kcal/mol}) = \frac{2.86 \times 10^{4}\ \text{kcal} \cdot \text{nm/mol}}{\text{Wavelength in nanometre}}]$$

4.1.3 Electromagnetic Spectrum

The total range of electromagnetic radiation (the range of all possible frequencies) is called the electromagnetic spectrum which is shown below (Figure 4.3)

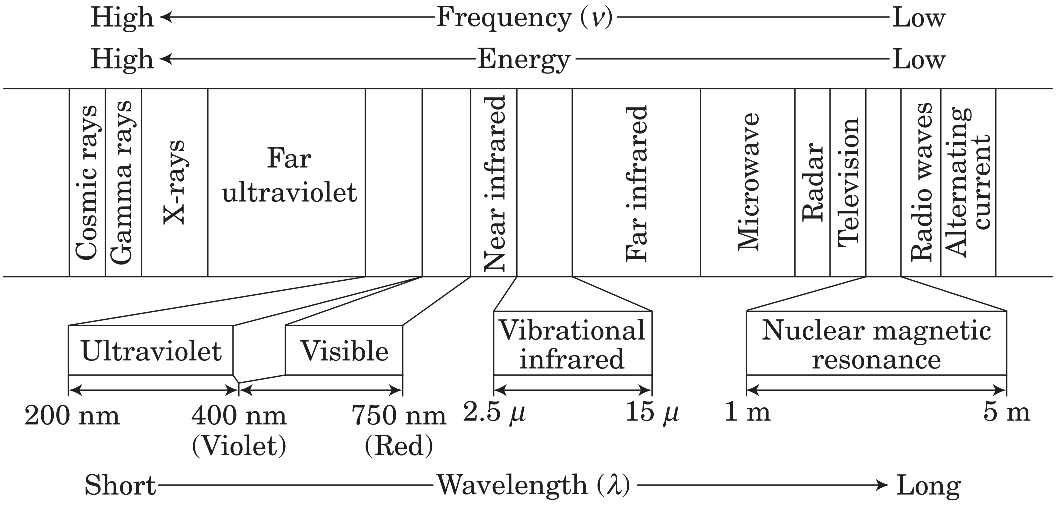


Figure 4.3 The electromagnetic spectrum

X-rays (very high energy) are so energetic that they can excite electrons, causing ionization. Energies in the ultraviolet-visible range causes change in electronic energy levels within the molecule. Infrared energies excite molecular vibrations and rotations. Microwave energies induces changes in the magnetic properties of unpaired electrons and radio-wave frequencies (very low energy) excite the nuclear spin transitions observed in nuclear magnetic resonance (NMR) spectroscopy.

The sensitivity limits of the human eye extend, from violet light (λ = 400 nm, 4×10^{-7} m) through the rainbow colours (i.e., indigo, blue, green, yellow and orange) to red light (λ = 750 nm, 7.5×10^{-7} m). Wavelengths less than 400 nm greater than 750 nm cannot be detected by the human eye. UV light ($\lambda < 400$ nm) can be detected on photographic film or in photoelectric cell, and infrared light ($\lambda > 750$ nm) can be detected either photographically or using a heat detector like a thermopile.

4.1.3.1 The Basic Process Used in Spectroscopy

The basic process involves in spectroscopy is the interaction between the electromagnetic radiation and molecules or ions. Such species possess certain quantized energy levels. That is, the excited states are separated from the ground states by discrete, specific amounts of energy. Therefore, a molecule or ion is not free to absorb all the frequencies within the spectrum of electromagnetic radiation. It can only absorb those frequencies corresponding to the energy (ΔE) required for excitation from one energy level to a higher one, i.e., $\Delta E = (E_2 - E_1) = h\nu$. This absorption is then measured in an instrument called a *spectrophotometer*.

4.1.3.2 Spectrum

The appearance of an ordered arrangement of things under consideration in accordance with a specific property may be called a spectrum. The spectrum of a visible or white light is an orderly arrangement of the constituent colours ranging from violet to red according to increasing wavelength. The electromagnetic spectrum is an orderly arrangement of the radiant energy according to wavelength ranging from short-waved cosmic rays to long-waves radio frequencies.

The field of spectroscopy is divided into emission and absorption spectroscopy. An emission spectrum is obtained by spectroscopic analysis of the radiant energy by an excited atom. The excitation of atoms can be brought about thermally (by heating the substance strongly) or electrically (by passing the electric discharge through the vapour of the substance at a very low pressure), and as a result, electrons in the ground state are promoted to metastable states. When electrons from metastable state jump to lower energy states, the absorbed energy is released as light. Fluorescent lights and colours obtained by heating salts of certain elements in a flame are common examples of emission spectra. A record of the amount of energy emitted by a sample as a function of its wavelength or frequency or wavenumber is called an *emission spectrum*. A record of the quantity of electromagnetic radiation absorbed by a sample as a function of its wave number or wavelength or frequency is said to be an *absorption spectrum*. A spectrophotometer usually analyzes the amount of transmitted light relative to the incident light of a given frequency. Automatic instruments gradually and continuously change the frequency and an automatic recorder plots a graph of the intensity of the transmitted or absorbed light versus frequency or wavelength, i.e., a spectrum. The spectrum of a compound, thus, represents a graph of either wavelength or frequency, continuously changing over a small portion of the electromagnetic spectrum versus either percent *transmittance* or *absorbance* (A). The percent transmittance (T) is the per cent of the intensity of the original radiation which passes through the sample.

$$\% \, T = \frac{\text{Intensity}}{\text{Original intensity}} \times 100$$

When a compound does not absorb any radiation at a particular wavelength, the percent transmission is 100 at that wavelength. Absorption of radiation at a particular wavelength leads to a decrease in the percent transmittance to appear in the spectrum as a dip, called a peak or absorption band. Absorbance is a measure of the absorption of radiation by a sample.

$$A = \log\left(\frac{\text{Original intensity}}{\text{Intensity}}\right)$$

Because of great difference in wavelength of different regions, it is not convenient to use the same unit throughout to specify a particular position in the spectrum. In the UV (200–400 nm) and visible (400–750 nm) regions, the wavelengths are expressed in nanometres (nm, 1 nm = 10^{-9} m), in the infrared region (4000 – 600 cm^{-1}), the wavelengths are expressed in microns (μ) or micrometres (μm, 1 μm = 10^{-6} m) or as the reciprocal wavelength in centimeters, $1/\lambda$, termed as the wavenumber $\bar{\nu}$. In the radio frequency region (NMR) absolute frequencies are used rather than wavenumbers. Thus, a wavelength of 5 m corresponds to a frequency of c/λ or 6×10^7 Hz (Hz = Hertz, defined as cycles per second) and can be written as 60 MHz.

4.1.3.3 Molecular Excitations and Spectroscopic Techniques

Depending upon the structure of molecule and v of the radiation absorbed by it, different categories of molecular excitation may occur and these are (a) *rotational*, (b) *vibrational*, and (c) *electronic*.

Rotational excitation involves rotation of atoms or groups about their bond axes within the molecule. Approximately 10^{-4} kcal/mol^{-1} of energy, which comes from photons or quanta of microwave radiation, is required for the rotational excitation. *Vibrational excitation* involves vibration of the constituent atoms of the molecule together with their rotational motion. About 1–10 kcal/mol^{-1} of energy, which comes from photons of infrared radiation, is sufficient for vibrational excitation of a molecule, i.e., for molecular transition between the two quantized vibrational energy levels. *Electronic excitation* involves promotion of an electron from a lower energy molecular orbital to a higher energy molecular orbital.

Usually 36–143 kcal/mol of energy, which comes from photons of ultraviolet (82–143 kcal/mol) and visible (36–82 kcal/mol) radiations, is required for electronic excitation of a molecule. Radio waves reorient nuclear spins ($\Delta E \sim 10^{-6}$ kcal/mol) a phenomenon which forms the basis of NMR spectroscopy.

For each electronic level within the molecule, there are a number of associated vibrational levels with less energy separations and in turn each vibrational level itself is associated with a set of rotational energy levels with even lesser energy separations.

The act of molecular absorption of energy in the ultraviolet, visible, infrared and radio frequency region at a definite wavelength is a function of a molecular structural feature, having the capability of absorbing specific photon. Consequently, it indicated the presence of a particular structure. Thus, the absorption of a radiant energy by a molecule, when recorded as spectrum, gives valuable information about its structure. The absorption spectrum for each molecule is unique because each molecule has its unique differences between its energy levels.

Three spectroscopic techniques used to identify organic compounds are infrared (IR) spectroscopy, ultraviolet-visible (UV-VIS) spectroscopy, and NMR spectroscopy. The general type of information each provides, are as follows:

(i) Infrared (IR) spectroscopy provides information about what functional groups are present.

(ii) Ultraviolet-visible (UV-VIS) spectroscopy (often called simply UV spectroscopy) provides information about the types of π-electron systems that are present.

(iii) NMR spectroscopy provides information on the number, connectivity and functional-group environment of all carbons and hydrogens in the molecule.

[A fourth physical technique, mass spectrometry, which allows us to determine molecular masses, is also widely used for structure determination. Mass spectrometry is not a type of absorption spectroscopy and is, thus, fundamentally different from NMR, IR and UV spectroscopy.]

To summarise:

1. Electromagnetic radiation is a form of energy with wave properties.
2. Wavelength (λ) and frequency (ν) are inversely proportional.
3. The wave number ($\overline{\nu}$) is the reciprocal of wavelength in cm.
4. Photons are discrete units or ‘packets’ of energy.
5. The energy (E) of a photon is equal to $h\nu$, where h is Planck’s constant and ν is frequency.
6. The electronic, vibrational and rotational energy levels of a molecule are quantized; only certain photons can be absorbed.
7. Electronic transitions require UV-VIS photons (λ = 200–400 nm); vibrational and rotational transitions require IR photons (λ = 2.5–15 μm)and changes in the magnetic properties of certain atomic nuclei involved in nuclear magnetic resonance (nmr) spectroscopy require radio waves (ν = 60–500 MHz).

8. Absorptions in the ultraviolet, visible, infrared and radio wave portions of the electromagnetic spectrum provide useful information about the structure of an organic compound.

SOLVED PROBLEMS

1. (a) List the colours in the spectrum of visible light in decreasing order of energy.

(b) Give the pairs of complementary colours.

Solution

Violet, Blue, Green, Yellow, Orange, Red

(a) $\xrightarrow{\text{Energy } (E) \text{ decreases}}$

(b) Violet and yellow; blue and orange; red and green.

2. Explain why absorption and not emission spectroscopy is used to study the spectra of organic compounds.

Solution The emission of radiation from an organic compound requires very high temperatures. Organic compounds are low melting and thus generally decompose at high temperatures. Because of this, emission spectroscopy is not used to study the spectra of organic compounds.

3. Calculate the frequency range of visible light if the wavelengths of violet and red light are 400 and 800 nm, respectively.

Solution

$$\text{Violet light : } \nu = \frac{c}{\lambda} = \frac{3\times10^{8}\,\text{ms}^{-1}}{400\times10^{-9}\,\text{m}} = 7.5\times10^{14}\ \text{s}^{-1} = 7.5\times10^{14}\ \text{Hz}$$

$$\text{Red light : } \nu = \frac{c}{\lambda} = \frac{3\times10^{8}\,\text{ms}^{-1}}{800\times10^{-9}\,\text{m}} = 3.75\times10^{14}\ \text{s}^{-1} = 3.75\times10^{14}\ \text{Hz}$$

Therefore, the frequency range of the visible light is 7.5×10^{14} Hz to 3.75×10^{14} Hz.

4. Calculate the frequency and wave number of infrared light of wavelength $\lambda = 10^4$ nm.

Solution

$$\text{The frequency, } \nu = \frac{c}{\lambda} = \frac{3\times10^{8}\,\text{ms}^{-1}}{10^{4}\times10^{-9}\,\text{m}} = 3\times10^{13}\ \text{s}^{-1} = 3\times10^{13}\ \text{Hz}$$

$$\text{The wave number, } \bar{\nu} = \frac{1}{\lambda} = \frac{1}{10^{4}\times10^{-9}\,\text{m}} = 1.0\times10^{5}\ \text{m}^{-1} = 1.0\times10^{3}\ \text{cm}^{-1}$$

5. Calculate the frequency of blue light having λ = 4800 Å.

Solution 4,800 Å = 4,800 × 10^{-8} cm = 4,800 × 10^{-10} m = 4.8 × 10^{-7} m

The frequency = $\nu = \frac{c}{\lambda} = \frac{3 \times 10^{8} \text{ms}^{-1}}{4.8 \times 10^{-7} \text{m}}$ = 0.625×10^{15} s^{-1} = 0.625×10^{15} Hz

6. Express each of the following in nanometres:
(a) 1 m (b) 10^3 m (c) 3.67 cm (d) 1.3×10^{-4} m

Solution

(a) 1 m = 10^9 nm

(b) 10^3 m = $10^3 \times 10^9$ nm = 10^{12} nm

(c) 3.67 cm = 3.67/100 m = $3.67 \times 10^{-2} \times 10^9$ nm = 3.67×10^7 nm

(d) 1.3×10^{-4} m = $1.3 \times 10^{-4} \times 10^9$ nm = 1.3×10^5 nm

7. (a) Light of what wavenumber has a wavelength of 2 μm?
(b) Light of what wavelength has a wavenumber of 100 cm^{-1}?
(c) Light of what frequency has a wavelength of 100 μm?

Solution

(a) 2 μm = 2×10^{-6} m = $2 \times 10^{-6} \times 10^2$ cm = 2×10^{-4} cm

$$\therefore \qquad \bar{\nu} = \frac{1}{2 \times 10^{-4} \text{cm}} = 5 \times 10^{-3} \text{cm}^{-1}$$

(b) $\lambda = \frac{1}{\bar{\nu}} = \frac{1}{10^2 \text{cm}^{-1}} = 10^{-2}$ cm

(c) λ = 100 μm = 100×10^{-6} m = 10^{-4} m

$$\therefore \qquad \nu = \frac{c}{\lambda} = \frac{3 \times 10^{8} \text{ms}^{-1}}{10^{-4} \text{m}} = 3 \times 10^{12} \text{ s}^{-1} \text{ or } 3 \times 10^{12} \text{ Hz}$$

8. A radio station transmits at approximately 0.81 MHz on medium wave. Calculate the wavelength of this transmission.

Solution The broadcast frequency is 0.81 MHz or 0.81×10^6 Hz or 0.81×10^6 s^{-1}.

$$\therefore \qquad \lambda = \frac{c}{\nu} = \frac{3 \times 10^{8} \text{ms}^{-1}}{0.81 \times 10^{6} \text{s}^{-1}} = 370 \text{ m}$$

9. Which is higher in energy per photon?
(a) Electromagnetic radiation with wavelength 10 or 7 μm.
(b) Electromagnetic radiation with wave number 500 cm or 10^3 cm^{-1}.
(c) Electromagnetic radiation with frequency 1.5×10^{15} or 1.5×10^8 Hz.

Solution High frequencies, large wave numbers and short wavelengths are associated with high energy.

Therefore, the electromagnetic radiations with (a) wavelength 7 μm, (b) wave number 10^3 cm^{-1}, and (c) frequency 1.5×10^{15} Hz are higher in energy per photon.

10. Calculate the amount of energy absorbed by one mole of a substance, when it interacts with ultraviolet light having $\nu = 1.5 \times 10^{-15}$ s^{-1} (Hz).

Solution $E = h\nu = (6.6 \times 10^{-34}\ \text{Js}) \times (1.5 \times 10^{15}\ \text{s}^{-1})$

$= 9.9 \times 10^{-19}\ \text{J}$

This is the amount of energy absorbed by one molecule interacting with the ultraviolet light.

Therefore, the amount of energy absorbed by one mole of a substance

$$= N_A \times 9.9 \times 10^{-19}\ \text{J}$$

$$= 6.02 \times 10^{23} \times 9.9 \times 10^{-19}\ \text{J mol}^{-1}$$

$$= 6 \times 10^{5}\ \text{J mol}^{-1}\ \text{(approx.)}$$

11. **Bond dissociation energies in organic molecules are around 400 kJ mol^{-1}. Calculate the frequency of the electromagnetic radiation required to dissociate bonds in organic molecules.**

Solution The energy absorbed by one molecule,

$$E = \frac{400\ \text{kJ mol}^{-1}}{6.02 \times 10^{23}\ \text{mol}^{-1}} = \frac{4 \times 10^{5}\ \text{J mol}^{-1}}{6.02 \times 10^{23}\ \text{mol}^{-1}} = 6.6 \times 10^{-19}\ \text{J}$$

Now, $E = h\nu$

or, $\nu = \dfrac{E}{h} = \dfrac{6.6 \times 10^{-19}\ \text{J}}{6.6 \times 10^{-34}\ \text{Js}} = 1.0 \times 10^{15}\ \text{s}^{-1}$ or 1.0×10^{15} Hz

STUDY PROBLEMS

1. Arrange the following radiations in order of increasing wavelength:

   Ultraviolet, Microwave, X-rays, Visible, Cosmic rays

2. Mention the ranges of electromagnetic radiation useful for UV and IR spectroscopy.
3. Which is the narrowest region in the electromagnetic spectrum?
   [**Hint:** Visible light]
4. Express 100 micrometres (a) in centimetres, (b) in angstroms (1 Å = 10^{-1} m), (c) in nanometres, (d) as wavenumbers.
5. Gamma rays vary in wavelength from 0.25 Å to 0.001 Å. What is the energy range of gamma rays?
6. One calorie is equivalent to 4.184×10^{7} ergs. Calculate the energy (in calories) corresponding to radiation with wavelength of 100 cm.
7. The amount of energy associated with one mole of photons is called one Einstein and equals to $Nh\nu$, where N is the Avogadro number. Calculate the value of Einstein for $3 \times 10^{3}\ \text{cm}^{-1}$ radiation.
8. The fundamental vibration of I_2 occurs at 214 cm^{-1}, while that of Cl_2 occurs at 565 cm^{-1}. Which vibration requires more energy?
9. A local radio station transmits (a) at approximately 95.5 MHz on its VHF (very high frequency) transmitter and (b) at 800 kHz on medium wave. Calculate the wavelengths of these transmissions.

10. Find out the corresponding wave number of two waves with $\lambda_1 = 10^5$ nm, and $\lambda_2 = 5$ µm, respectively.

11. Blue light has $\bar{\nu} = 20{,}800$ cm^{-1}. Calculate ν in Hz and λ in nm.

4.2 ULTRAVIOLET SPECTROSCOPY

The absorption of UV-VIS radiation by a molecule causes transfer of an electron from one electronic state to the next, i.e., it leads to transition among the electronic energy levels of the molecule, and because of this, it is often called *electronic spectroscopy*. Light of wavelength between 400 and 800 nm is visible. Just beyond the violet end of the visible spectrum ($\lambda = < 400$ nm) lies the ultraviolet region. As is typical of most UV spectra, the absorption is rather broad and is often spoken of as a "band" rather than a "peak". A typical UV spectrum shows only a few broad humps. In a transition to a higher electronic level, a molecule can go from any of a number of sub-levels—corresponding to various rotational and vibrational states—to any of a number of sub-levels. As a result, the UV absorption bonds are broad. One can conveniently describe such a spectrum in terms of the position of top of the hump (λ_{max}) and the intensity of the absorption (ε_{max}, the extinction coefficient).

The ultraviolet and visible spectroscopy is primarily used to measure the extent of the multiple bond or aromatic conjugation within molecules. Electronic spectroscopy can, in general, differentiate conjugated diens from nonconjugated dienes, conjugated dienes from conjugated trienes, α,β-unsaturated ketones from their $\beta\gamma$-analogs, etc. Since the degree of conjugation may suffer in strained molecules due to loss of π-orbital overlap, electronic spectroscopy may be used to study such strain by correlating the change in spectrum with angular distortion. The position of absorption may also be influenced by substituents.

An instrument for measuring the interaction of molecules with ultraviolet and visible light is called UV-VIS spectrometer. In UV spectroscopic analysis, the samples are usually scanned in dilute solutions. The solution must be placed in some suitable container that is transparent to light in the region being studied. Although ordinary glass is satisfactory for work in the visible region, glass absorbs ultraviolet light strongly; hence quartz (silica) cells must be used. The most commonly used cells have 1.0 cm path length. The most suitable source of light in the ultraviolet region (200–400 nm) is the hydrogen-discharge lamp. A tungsten-filament lamp is usually used for the visible region (400–800 nm) of the spectrum. Most spectrophotometers are double-beam instruments. The primary source of light is split into two beams, one of which passes through a cell containing the reference solvent. The spectrophotometer electronically subtracts the absorption of the solvent in the reference beam from the absorption of the solution in the sample beam. Thus, effects owing to absorption of light by the solvent are minimized. The ordinary VIS-UV spectrophotometer provides acceptable spectra over the range 220–800 nm. Better instruments have mechanical improvements that extend the short-wavelength range to about 185 nm. The major limitation in the short-wavelength range is the presence of air in the instrument. Oxygen absorbs strongly at about 200 nm and below; frequently the range of the instrument can be extended by flushing the instrument with nitrogen, which absorbs strongly at about 150 nm and below. The technique of using an evacuated spectrophotometer enables the range below 200 nm to be studied. This region is frequently called the *vacuum ultraviolet region*.

The plotting of UV or electronic spectra is done by recording wavelength (on the horizontal axis) versus absorbance (on the vertical axis). The absorbance A (often called optical density, 0D) is given by the expression:

$$A = \log \frac{I_0}{I}$$

where I_0 = intensity of incident light or the intensity of light after passing through the reference cell, I = intensity of the transmitted light, i.e., the light after passing through the sample.

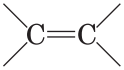
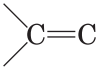
4.2.1 Visible Spectrum and Complementary Colours

When a substance is exposed to the visible region of the electromagnetic radiation, i.e., to white light ($\lambda = 400$–800 nm), the light may be completely reflected or completely absorbed and as a consequence, the substance appears white or black, respectively. If a certain portion of the light is absorbed and the rest reflected, the substance has the colour of the reflected light. If only a single band is absorbed by the substance, it has the complementary colour of the absorbed band (which is actually the combination of the reflected colours). Again, if a substance reflects only a single band and absorbs the rest of the visible light, the substance will have the colour of the reflected band. However, the former mode of absorption is more common. Thus, a substance can appear blue because it absorbs the yellow band of the spectrum only (blue in the complementary colour of yellow) or because it absorbs all the visible spectrum except blue.

Wavelength region (nm)	Colour absorbed	Complementary colours (visible)
400–435	Violet	Yellow-green
435–480	Blue	Yellow
480–490	Green-blue	Orange
490–500	Blue-green	Red
500–560	Green	Purple
560–580	Yellow-green	Violet
580–595	Yellow	Blue
595–605	Orange	Green-blue
605–750	Red	Blue-green

4.2.2 Certain Terms Involved in UV Spectral Analysis

Certain phenomena in UV spectroscopy is expressed conventionally by using some old terminologies. These are as follows:

1. Chromophore The term chromophore (originated from the Greek *chromophoros* meaning *colour carrier*) was originally applied to the system responsible for imparting colour to a compound. Thus, the nitro group is the chromophore which imparts yellow colour to nitro compounds. Similarly, the aryl conjugated azo group is a chromophore for providing colour to azo dyes. Now, the term chromophore is used in a broader way and in fact, a chromophore in general is a covalently unsaturated group that absorbs electromagnetic radiation, whether or not a 'colour' is thereby produced. Thus, a chromophoric group offers a characteristic absorption in the ultraviolet or visible region. Some important chromophoric groups are: , —C≡C—, , —COOH, —CO_2Et, –NO_2, —N═N—, quinonoid structure, etc.

2. Auxochrome An auxochrome is usually a saturated functional group with nonbonded electrons which does not itself act as a chromophore but, when attached with a chromophore, enhances the colour-imparting properties of the chromophore by bringing about a shift of the absorption bond (λ_{max}) to longer wavelength with increasing intensities. This is due to enhanced conjugative effect of auxochromes imparted to the chromophores by delocalization of the unshared electrons in the chromophore orbitals. Examples of some auxochromes are $—\ddot{\underset{..}{O}}H, —\ddot{\underset{..}{O}}R, —\underset{..}{N}H_2, —\ddot{N}R_2, —\ddot{\underset{..}{S}}H, —\ddot{\underset{..}{F}}:, —\ddot{\underset{..}{Cl}}:$, etc. In a very real sense, the auxochrome is considered as a part of a new extended chromophore and the term 'auxochrome' is seldom used in spectroscopy.

3. Bathochromic shift (red shift) A shift of absorption maximum (λ_{max}) towards longer wavelength, i.e., towards the red end of the spectrum by changing the nature (polarity) of the solvent, pH of the medium or structure of the compound to one with increased conjugation is called bathochromic shift or red shift. For example, the λ_{max} for $\pi—\pi^*$ transition of carbonyl compounds shows a bathochromic or red shift by changing the solvent from a nonpolar to a polar one. Similarly, phenol (PhOH) exhibits a bathochromic shift by changing the solution from acidic to alkaline, i.e., by increasing pH of the medium.

4. Hypsochromic shift (blue shift) A shift of absorption maximum (λ_{max}) towards shorter wavelength, i.e., towards the blue end of the spectrum is called hypsochromic shift or blue shift. This shift may be caused by decreasing conjugation, changing the polarity of the solvent or changing the pH of the medium. For example, the λ_{max} for $n–\pi^*$ transition of carbonyl compounds shows a hypsochromic shift or blue shift by changing the solvent from nonpolar to polar, whereas aniline shows a hypsochromic shift by decreasing the pH of the medium (alkaline or neutral to acidic).

5. Hyperchromic effect The increase in intensity of absorption (ε_{max}) caused by changing the nature of the solvent, pH of the medium or structure of the substrate is called hyperchromic effect.

6. Hypochromic effect The decrease in intensity of absorption maximum ($\varepsilon_{\max}$) by changing the nature of the solvent, pH of the medium or structure of the substrate is known as hypochromic effect.

These shifts/effects can be shown by the following diagram (Figure 4.4):

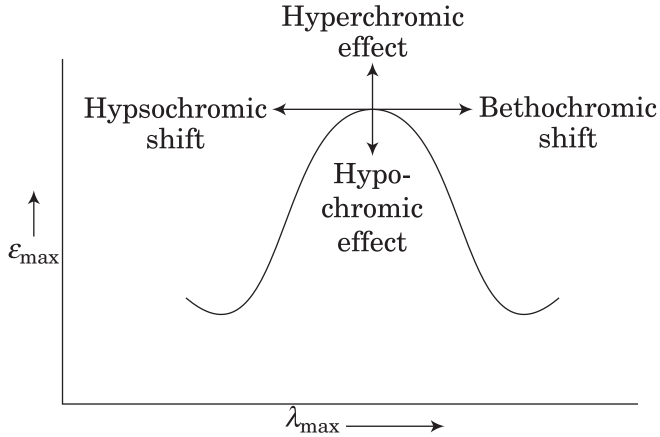


Figure 4.4 Absorption and intensity shifts

4.2.3 Theory of Electronic Spectroscopy

When a molecule absorbs light in the UV and visible region, it gets excited and suffers from a change in electronic states. The change involves transition of one electron (according to the first approximation of the Franck-Condon principle) from the occupied bonding (σ or π) or non-bonding (n) molecular orbitals of lower energy in the ground state to unoccupied antibonding (σ^* or π^*) molecular orbitals of higher energy in the excited state. Hence, the electronic transitions, designated by an arrowhead (→), that may involve in UV and visible regions, are $\sigma \rightarrow \sigma^*$ ('sigma to sigma star'), $n \rightarrow \sigma^*$, $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$.

The sequence of electronic orbital energies, showing different kinds of transitions may be shown as in Figure 4.5.

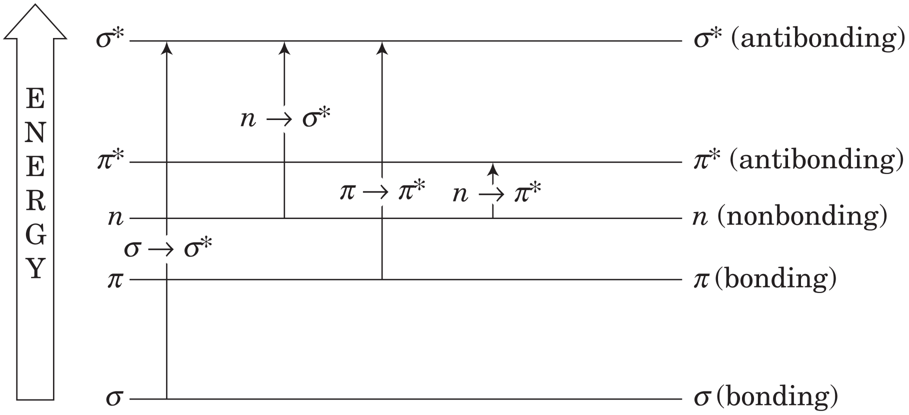


Figure 4.5 Electronic energy levels and transitions

Hence, the energy required for various transitions obey the following general order:

$$\sigma \rightarrow \sigma^* > n \rightarrow \sigma^* > \pi \rightarrow \pi^* > n \rightarrow \pi^*$$

The wavelength of light absorbed depends on the energy difference between the ground and the excited state. The relation between the wavelength of light and the amount of energy absorbed is given by the following equation:

$$\lambda = hc/\Delta E$$

This relation shows that the greater the difference between the energies of the two electronic states (ΔE), the shorter is the wavelength of the light absorbed and vice versa.

The various electronic transitions are discuss below:

1. $\sigma \rightarrow \sigma^*$ transition Transition of an electron from a low-energy bonding σ-orbital to a high-energy antibonding σ-orbital (σ^*) is referred to as a $\sigma \rightarrow \sigma^*$ ('sigma to sigma star') transition. Since σ-bonds are, in general, very strong, this is a high-energy process requiring very short wavelength (~150 nm) ultraviolet light and occurs at far UV region. Since oxygen of air absorbs light energy below 200 nm, this region is not readily accessible by ordinary spectrophotometer. Vacuum spectrophotometer is used to record far UV spectrum. $\sigma \rightarrow \sigma^*$ transitions (C—H and C—C) are possible only in alkanes because only σ and no other molecular orbitals are involved in those compounds. Ethane; for example, has a λ_{max} 135 nm (C—C).

2. $n \rightarrow \sigma^*$ transition An $n \rightarrow \sigma^*$ transition represents the transition of one electron of a lone pair (i.e., a nobonding pair of electrons to an antibonding σ orbital, i.e., σ^*. This transition requires comparatively less energy than $\sigma \rightarrow \sigma^*$ transition. This is an 'allowed' transition and give rise to a strong absorption band. Molecules containing nonbonding electrons on oxygen, nitrogen, sulphur, or halogen atoms and no π MO's are capable of showing mainly $n \rightarrow \sigma^*$ transitions, which can be recorded at ordinary UV region. For example, alkyl chlorides (RCl), alkyl bromides (RBr), alkyl iodides (RI), alcohols (ROH), and a amines (RNH_2) absorb at 170–175, 200–210, 255–260, 180–185 and 190–200 nm, respectively.

3. $\pi \rightarrow \pi^*$ transition A transition in which a bonding π electron is excited to an antibonding π orbital is referred to as a $\pi \rightarrow \pi^*$ transition. Depending on the system involved this transition required more, or less, energy than $n \rightarrow \sigma^*$ transition. This is an 'allowed' transition which gives rise to a strong absorption band. This transition is available in compounds (containing π MO's) like alkenes, aromatic compounds, carbonyl compounds, etc. Ethylene, for example, has λ_{max} 175 nm. In HCHO the most intense band around 160 nm is due to the $\pi \rightarrow \pi^*$ transition.

In conjugated dienes, the π orbitals of the separate alkene groups combine to form new orbitals – two bonding orbitals designated as π_1 and π_2 (or ψ_1 and ψ_2) and two antibonding orbitals designated as π_3^* and π_4^* (or ψ_3^* and ψ_4^*). The relative energies of these new orbitals are shown in Figure 4.6 and it becomes apparent that among all possible transitions (π_1 to π_2 to π_3^* or π_4^*) the $\pi_2 \rightarrow \pi_3^*$ transition, i.e., promotion of an electron from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO), requires lowest energy and in fact, it is much lower than that required for the $\pi \rightarrow \pi^*$ transition of an unconjugated alkene. This new $\pi \rightarrow \pi^*$ transition of much lower energy is actually possible as a result of conjugation. The more the conjugation is extended, the more the HOMO–LUMO energy gap decreases, i.e., the more the λ_{max} shifts to longer wavelength. Thus, the value of λ_{max} increases on going from left to right in the following series:

	$CH_2{=}CH_2$	$CH_2{=}CH{-}CH{=}CH_2$	$CH_2{=}CH{-}CH{=}CH{-}CH{=}CH_2$
	Ethylene	1,3-Butadiene	1,3,5-Hexatriene
$\lambda_{max}\,(\pi \rightarrow \pi^x)$:	175 nm	217 nm	258 nm

Conjugated carbonyl compounds (α, β-unsaturated aldehydes and ketones) also have high-intensity absorptions resulting from the transition of an electron from π_2 to $\overset{*}{\pi_3}$. These $\pi \rightarrow \pi^*$ transitions occur at almost exactly the same wavelength as those for the corresponding diens. For example, acraldehyde ($CH_2{=}CH{-}CHO$) has a λ_{max} 218 nm. As in the case of polyenes, the wavelength of light absorbed by unsaturated carbonyl compounds increases as the chain of conjugation increases. The value of λ_{max}, for example, increases on going from left to right in the following series:

	$CH_3CH{=}CHCHO$	$CH_3(CH{=}CH)_2CHO$	$CH_3(CH{=}CH)_3CHO$
$\lambda_{max}\,(\pi \rightarrow \pi^*)$:	220 nm	270 nm	312 nm

4. $n \rightarrow \pi^*$ transition An $n \rightarrow \pi^*$ transition represents the transition of one electron of a lone pair (i.e., a nonbonding pair of electrons) to an antibonding π orbital (i.e., π^*). This transition requires least amount of energy among the possible transitions and therefore, this transition gives rise to an absorption band at longer wavelengths. This transition is however, 'forbidden' in symmetry terms because the axis of p orbital is oriented along the nodal plane of n orbital. The relative energies of molecular orbitals that most concern us are illustrated in Figure 4.6.

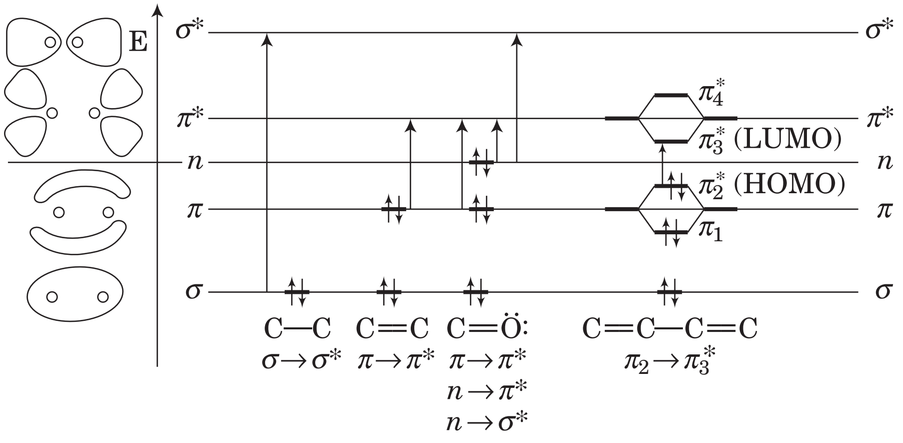


Figure 4.6 Relative energies of orbitals most involved in electronic spectroscopy of organic molecules

4.2.4 Laws of Light Absorption – Beer's and Lambert's Laws

The UV spectrum is generally recorded as a plot of **absorbance** (sometimes called **optical density**, abbreviated OD) versus wavelength. The absorbance is a measure of the amount of radiant energy absorbed. If the radiation entering a sample has intensity I_0, and the light emerging from the sample has intensity I, then the absorbance A may be defined as the logarithm of the ratio I_0/I:

$$A = \log\left(\frac{I_0}{I}\right)$$

From this equation, it becomes clear that the more the radiant energy is absorbed, the larger is the ratio I_0/I, and the greater is the absorbance.

Beer's and Lambert's laws govern the absorption of light by molecules. Beer's law relates the absorption to the concentration of the absorbing compound, and Lambert's law relates the total absorption to the optical path length, i.e., the length of the light path through the sample.

The relationship between absorbance, concentration, length of the light path, and molar absorptivity, known as the **Beer–Lambert Law**, is given by

$$A = c\, l\, \varepsilon, \text{ where}$$

A = absorbance of the solution

c = concentration of the sample (in mol l^{-1} or mol dm^{-3})

l = length of the light path through the sample (in cm or m $\times 10^{-2}$), and

ε = molar absorptivity (formerly called the molar extinction coefficient (in l mol^{-1} cm^{-1} or m^2 $mol^{-1} \times 10^{-2}$)

The molar absorptivity, ε, is constant for a particular compound at a given wavelength, and is most commonly expressed as ε_{max}—the molar absorptivity at an absorption band maximum. In fact, it is the absorbance that would be observed for a 1.00 M solution in a cell with a 1 cm path length. ε_{max} is normally expressed without units. Since values for ε_{max} can be very large, an alternative convention is to use its logarithm (to the base 10), $\log_{10} \varepsilon_{max}$. In fact, the intensity, i.e., the height of the peak is a measure of transition probability and the peaks with low ε values often arises from transitions which are normally 'forbidden'. The wavelength corresponding to a given ε_{max} is termed as λ_{max}. Both λ_{max} and ε_{max} are affected by the solvent, which is therefore included when reporting UV–VIS spectroscopic data. Therefore, the UV spectrum of acetone in hexane would be reported as λ_{max} = 195 nm (ε_{max} = 9000, hexane). A typical UV spectrum is shown is Figure 4.7.

Although the UV spectrum is generally recorded as a plot of absorbance versus wavelength, it is customary to then replot the data with either ε or log ε plotted on the y-axis and wavelength plotted on the x-axis.

$$\varepsilon_{max} = \frac{\text{Absorbance} \times \text{Molecular weight} \times 100}{\text{Weight (mg) of the compound in 100 ml} \times \text{Path length (cm)}}$$

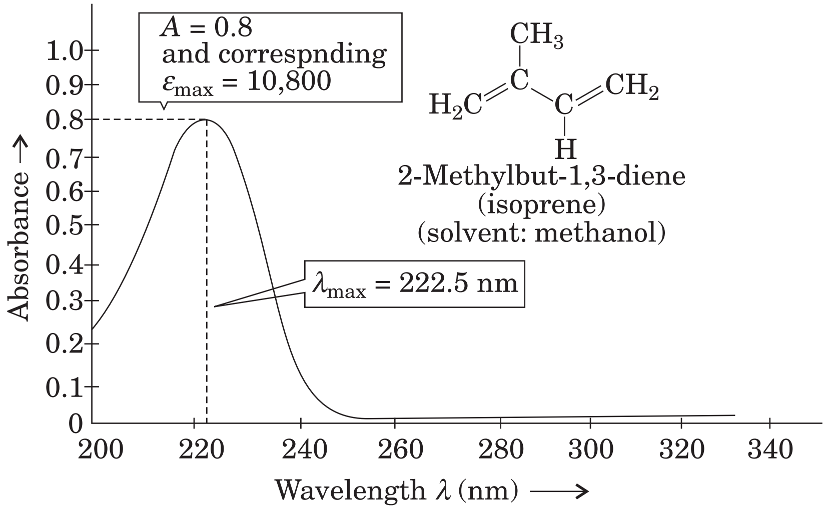


Figure 4.7 UV spectrum of 2-methyl-1,3-butadiene

By using the above relation, the value of $\varepsilon_{\max}$ of isoprene has been calculated to be 10,800 (absorbance = 0.8, mol. wt. = 68, path length = 1 cm). The UV spectrum is usually taken by using a very dilute solution ($10^{-5} - 10^{-6}$ M) of the compound in a solvent which is transparent above 200 nm.

4.2.5 Choice of Solvent

Very dilute solutions are usually used to measure electronic spectra. The solvent used must be transparent within the wavelength range being examined. The lower-wavelength limits for common spectroscopic-grade solvents are shown in Table 4.1. Below these limits, the solvents shown excessive absorbance and sample absorbance will not be recorded linearly. The solvents are listed in the table in an approximate order of preference, and, in fact, a choice of water, ethanol and hexane will meet most requirements.

Table 4.1 Solvents for UV spectroscopy

Solvent	Lower wavelength limit/nm
Water	205
Ethanol (95% or absolute)	210
Hexane	210
Cyclohexane	210
Methanol	210
Diethyl ether	210
Acetonitrile	210
Tetrahydrofuran	220
Dichloromethane	235
Chloroform	245
Carbon tetrachloride	265
Benzene	280

4.2.6 Principal Characteristics of a UV Absorption Curve

The principal characteristics of a UV absorption curve are as follows:

(a) The position of absorption The position of absorption is indicated by the $\lambda_{\max}$ value whose energy is equal to that required for the promotion of an electron from the ground state energy level to the excited state energy level.

(b) The intensity of absorption The intensity of absorption, indicated by $\varepsilon_{\max}$, is proportional to the probability that the transition will take place and the target area of the absorbing system, i.e., the chromophore. It can be shown that

$$\varepsilon_{\max} = 0.87 \times 10^{20} \, P.\mathbf{a}$$

where P is the transition probability (with values from 0 to 1) and **a** is the target area of the absorbing system. The transition probability in its turn is proportional to the square of the transition moment which is measured by the magnitude of the change in molecular dipole moment brought about by transition. If a molecule has a large transition moment, its intensity of absorption will be high. The transitions with values of $\varepsilon_{\max}$ more than 10^4 are usually called *allowed transitions*. They generally arise due to $\pi \rightarrow \pi^*$ transitions. Since, both of the orbitals π and π^* lie in the same plane, the transition is geometrically favourable. In 1,3-butadiene, the absorption at 217 nm, $\varepsilon_{\max}$ 21,000 is an example of allowed transition. The transitions with values of $\varepsilon_{\max}$ less than 10^4 are usually called *forbidden transitions*. They generally arise due to $n \rightarrow \pi^*$ transitions. These two orbitals orbitals are perpendicular to each other. So the jump of an electron from nMO to π^*MO is geometrically poor and its probability is thus very low. The $n \rightarrow \pi^*$ transition near 300 nm in the case of carbonyl compounds with $\varepsilon_{\max}$ values of the order 10–100 is an example of forbidden transition. The allowedness of electronic transitions is related with the geometries of the lower- and higher-energy molecular orbitals, the symmetry of the molecule as a whole, and the orientation of the electric dipole of the incident light that might induce the transition. Symmetrical molecules have more restrictions on their electronic transitions than have less symmetrical molecules. For example, benzene is a highly symmetrical molecule. Thus, many restrictions apply to the electronic transitions of the benzene molecule, and so, its electronic absorption spectrum is simple. For a totally unsymmetrical molecule, no symmetry restrictions apply to the electronic transitions, so that transitions may be observed among all of its molecular orbitals except among filled orbitals.

4.2.7 Types of Absorption Bands in UV Spectroscopy

The four types of absorption bands that originate as a result of the possible electronic transitions in a compound, are as follows:

(a) K-band (K is the first letter of the Geman word *Konjugierte*) This type of band arises due to $\pi \rightarrow \pi^*$ transition in a compound containing a conjugated system such as dienes, polyenes, enones, etc. K band also appears in an aromatic compound substituted by a chromosphere. The intensity of the K-band is usually more than 10^4.

(b) R-band (R is the first letter of the German word *Radikalartig*) This type of band arises due to $n \rightarrow \pi^*$ transition of a single chromophoric group having at least one unshared pair of electrons on a hetero atom. The intensity of R-band is usually less than 100.

(c) B-band (B stands for Benzenoid) This type of band arises due to vibrational effects on the $\pi \rightarrow \pi^*$ transition in aromatic or heteroaromatic molecules. Benzene shows a broad absorption band in the ordinary UV region between 230 and 270 nm. When a chromophoric group is attached to the benzene ring, the B-band is observed at a longer wavelength than the more intense K-band. In styrene, for example, the K-band appears at $\lambda_{\max} = 244$ nm, $\varepsilon_{\max} = 12{,}000$ and the B-band appears at $\lambda_{\max} = 282$ nm, $\varepsilon_{\max} = 450$.

(d) E-band (E stands for Ethylinic) This type of band arises due to oscillations of electrons in the three ethylinic bands which are in closed cyclic conjugation in the benzenoid system. This is further characterized as E_1 and E_2-bands. E_1 and E_2 bands of benzene appear at 184 nm ($\varepsilon_{\max}$ 47,000) and 202 nm ($\varepsilon_{\max}$ 7,000), respectively. The E_1-band which appears at shorter wavelength is usually more intense than the E_2-band for the same compound which appears at longer wavelength.

4.2.8 Various Structural Effects that have Remarkable Influence on the Electronic Spectra

The following structural effects have remarkable influence on the electronic spectra:

(a) Resonance effect Resonance stabilizes both the ground and the excited state of a species. However, the stabilization may be greater in one than in the other. If the excited state is more stabilized by resonance in comparison to the ground state, the electronic excitation energy (ΔE) will be lower than what it would have been if the ground state is more stabilized by resonance relative to the excited state and consequently, the $\lambda_{\max}$ value of the former case will be greater than that of the later case. Hence, it is not the magnitude of resonance energy but whether resonance stabilizes primarily the excited state or the ground state that decides the effect of resonance on electronic spectra. Conjugate systems have increased resonance stabilization in the excited states. Greater number of charge separated resonance structures that can be written for the conjugated systems perhaps brings about more resonance stabilization of the excited state which is more polar than the ground state. Thus, a conjugated system has lower ΔE value and hence larger $\lambda_{\max}$ value than a similar non-conjugated system.

An alternate interpretation is as follows. As resonance effect (which depends upon conjugation) increases, $\Delta E_{\text{HOMO} \rightarrow \text{LUMO}}$ decreases and consequently, $\lambda_{\max}$ increases.

(b) Hyperconjugative effect Hyperconjugation or no-bond resonance also brings stability to the excited state more than the ground state and it has the same effect on $\lambda_{\max}$ as resonance has.

An alternate interpretation is as follows. Since in hyperconjugation the σ electrons of the C—H bond interact with the chromophoric group, the conjugation becomes extended. As a result of this, $\Delta E_{\text{HOMO} \rightarrow \text{LUMO}}$ decreases and consequently $\lambda_{\max}$ increases.

(c) Steric effect If steric effect reduces the coplanarity of the system, delocalization of π electrons becomes inhibited and as a consequence, the length of conjugation decreases. Because of this decreased conjugation, $\Delta E_{\text{HOMO} \to \text{LUMO}}$ increases, and consequently, $\lambda_{\max}$ decreases.

(d) Hydrogen-bonding effect Owing to greater polarity, the strength of intramolecular hydrogen bonding increases in the excited state relative to the ground state and as a result, the excited state is stabilized by intramolecular H-bonding more than the ground state. Hence, the electronic excitation energy (ΔE) of a molecule possessing internal H-bond will be lower and consequently, the $\lambda_{\max}$ value will be higher than what it would have been if there were intermolecular hydrogen bonding.

4.2.9 Solvents Effects

Polarity of solvents has a profound effects on the position and intensity of an absorption band. Both $\pi \to \pi^*$ and $n \to \pi^*$ transitions are influenced by changing the polarity of the solvent. Compounds like conjugated dienes and aromatic hydrocarbons experience a very little solvent shift, while α,β-unsaturated carbonyl compounds show two different solvent shifts (i) the $\pi \to \pi^*$ band moves to longer wavelength (red shift), while (ii) the $n \to \pi^*$ band moves to shorter wavelength (blue shift). A polar solvent stabilizes π, π^* and n orbitals by solvation. The stabilization of nonbonding orbitals is particularly pronounced with H-bonding solvents (such as ethanol or water), and π^* orbitals are more stabilized by solvation than are π orbitals, presumably because π^* orbitals are relatively more polar than π orbitals. The net result is that the energy of $\pi \to \pi^*$ transition becomes less with solvation (red shift), while the energy of $n \to \pi^*$ transition becomes greater with solvation (blue shift). This can be expressed in the form of an energy diagram as follows (Figure 4.8):

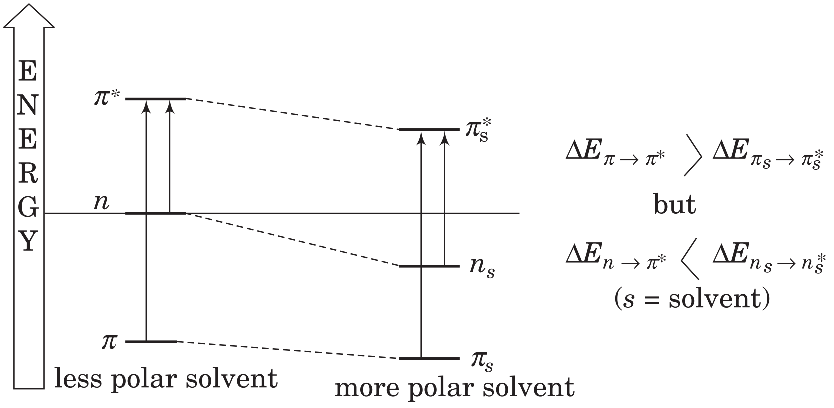

ENERGY
π^*
n
π
π_s^*
n_s
π_s
less polar solvent
more polar solvent
$\Delta E_{\pi \to \pi^*} > \Delta E_{\pi_s \to \pi_s^*}$
but
$\Delta E_{n \to \pi^*} < \Delta E_{n_s \to n_s^*}$
(s = solvent)

Figure 4.8 **Effect of solvation on the relative energies of orbitals and transitions in α,β-unsaturated carbonyl compounds**

The effect of solvent polarity on the spectrum of mesityl oxide, for example, may be shown in Table 4.2.

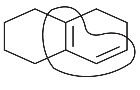
Table 4.2 Effect of solvent polarity on the λ_{max} of mesityl oxide ($CH_3CH{=}CHCOCH_3$)

Polarity and H-bond forming ability increases downward	**Solvent**	λ_{max} ($\pi \rightarrow \pi^*$)	λ_{max} ($n \rightarrow \pi^*$)
	n-Hexane	230 nm	327 nm
	Ether	230 nm	326 nm
	Ethanol	237 nm	315 nm
	Water	245 nm	306 nm

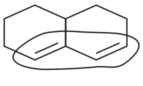
[**Alternate explanation:** The excited state in most $\pi \rightarrow \pi^*$ transitions is more polar than the ground state. Therefore, a polar solvent stabilizes the excited state more strongly than it does the ground state, by dipole-dipole interactions. As a result, the energy of the excited state is decreased more than that of the ground state, shifting the transition to longer wavelength (red shift). On the other hand, the ground state in most $n \rightarrow \pi^*$ transitions is more polar than the excited state. H-bonding solvents, in particular, as well as aprotic polar solvents, interact more strongly with the unshared pair of electrons in the ground state lowering its energy more than in the excited state. The transition, therefore, requires more energy and the absorption occurs at a shorter wavelength (blue shift)].

4.2.10 Woodward-Fieser Rules for Calculating λ_{max} for $\pi \rightarrow \pi^*$ Transitions in Conjugated Dienes, Trienes and Polyenes

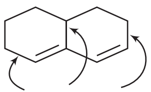
That the diene absorption is influenced by structure in a surprisingly regular way was first observed by R.B. Woodward. He formulated certain empirical rules for calculating λ_{max} values for substituted conjugated dienes, trienes, and polyenes. These rules were later modified by L.M. Fieser and M. Fieser. According to these rules, each type of diene (acyclic, heteroannular or homoannular) has a certain fixed basic value and the value of absorption maximum (λ_{max}) depends upon: (i) the number of alkyl substituents or ring residues on the double bond, (ii) the number of double bonds which extend conjugation and (iii) the presence of polar groups like —Cl, —Br, —OR, —SR, etc. A ring residue is a C—C bond, not a part of the conjugated polyene system but attached to any one of the carbon atoms of the conjugated system.



Homoannular diene



Heteroannular diene

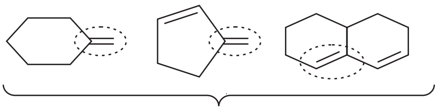


Ring residues

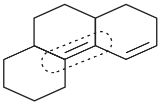
The various rules for calculating λ_{max} for $\pi \rightarrow \pi^*$ transitions (K-band) in conjugated dienes and trienes (in ethanol) are summarized in Table 4.3.

Table 4.3 Conjugated dienes and trienes (in ethanol) λ_{max} for $\pi \to \pi^*$ transitions; ε_{max} 6,000–35,000

Base value for acyclic and heteroannular dienes	215 nm
Base value for homoannular dienes	253 nm
Base value for acyclic trienes	245 nn
Increment for each substituent	
—R (alkyl) or ring residue	5 nm
—OR (alkoxy)	6 nm
—SR (thioether)	30 nm
—Cl (chloro), —Br (bromo)	5 nm
—OCOR (acyloxy)	0 nm
—NR_2 (*N*, *N*-dialkylamine)	60 nm
—CH═CH— (additional conjugation)	30 nm
Cross conjugation	0 nm
One double bond exocyclic to one ring	5 nm
One double bond exocyclic to two rings	10 nm
Solvent shift	0 nm

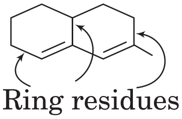


One double-bond exocyclic to one ring



One double-bond exocyclic to two rings

The method can be illustrated by the following three worked examples:

1. 

It is a heteroannular diene with one alkyl substituent and three ring residues.

Base value = 215 nm

Increments for:

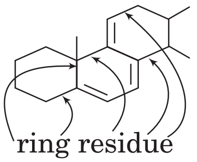
One alkyl substituent = 5 nm

Three ring residues (3 × 5 nm) = 15 nm

One exocyclic double bond = 5 nm

Calculated λ_{max} = 240 nm

This is within 2 nm of the observed value.

2. 

This is a homoannular diene with five ring residues, three exocyclic double bonds and one conjugated C═C.

Base value = 253 nm

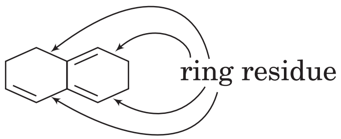
Increments for:

Five ring residues (5 × 5 nm) = 25 nm

Three exocyclic double bonds (3 × 5 nm) = 15 nm

One additional conjugation = 30 nm

Calculated λ_{max} = 323 nm

3. 

It must be considered as a homoannular diene with four ring residues and two exocyclic double bond. The third double bond is cross conjugated with the homoannular diene system and therefore, it has no contribution to λ_{max}.

Base value = 253 nm

Increments for:

Four ring residues (4 × 5 nm) = 20 nm

Two exocyclic double bonds (2 × 5 nm) = 10 nm

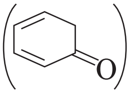
Calculated λ_{max} = 283 nm

4.2.11 Woodward–Fieser Rules for Calculating λ_{max} for $\pi \rightarrow \pi^*$ Transition in α,β-unsaturated Carbonyl Compounds

The method of use is similar to that for conjugated dienes, the only two variants are: (i) the distinction between α and β substituents and (ii) the importance of solvent shifts. Table 4.4 shows the correlations that can apply to α,β-unsaturated carbonyl compounds.

Table 4.4 α,β-Unsaturated carbonyl compounds (in ethanol); λ_{max} for $\pi \rightarrow \pi^*$ transitions; ε_{max} 4,500–20,000

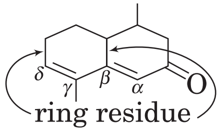
Base values	Ketones	$-\overset{\beta}{\overset{\vert}{C}}=\overset{\alpha}{\overset{\vert}{C}}-\overset{O}{\overset{\Vert}{C}}-$	acylic or 6-ring cyclic	215 nm
			5-ring cyclic	202 nm
	Aldehydes	$-\overset{\vert}{C}=\overset{\vert}{C}-CHO$		207 nm
	Acid and esters	$-\overset{\vert}{C}=\overset{\vert}{C}-CO_2H(R)$		197 nm

Increment for each substituent		
—R (alkyl) or ring residue	α β γ and higher	10 nm 12 nm 17 nm
—OH (hydroxy)	α β, γ δ	35 nm 30 nm 50 nm
—OR (alkoxy)	α β γ δ	35 nm 30 nm 17 nm 31 nm
—OCOR (acyloxy)	$\alpha, \beta, \gamma, \delta$	6 nm
—SR (thioether)	only β	80 nm
—Cl (chloro)	α β, γ, δ	15 nm 12 nm
—Br (bromo)	α, γ, δ β	25 nm 30 nm
$—NH_2$, —NHR, $—NR_2$ (amino)	only β	95 nm
—CH═CH— (additional conjugation)		30 nm
Homodiene system 		39 nm
One double-bond exocyclic to one ring		5 nm
One double-bond exocyclic to two rings		10 nm
Solvent corrections		
Above values are shifted to longer wavelength in more polar solvents (e.g., H_2O) and to shorter wavelength in less polar solvents (e.g., $CHCl_3$). For common solvents the following corrections must be applied in computing λ_{max}.		
Water	+8 nm	
Methanol	0 nm	
Chloroform	–1 nm	
Dioxan	– 5 nm	
Diethyl ether	–7 nm	
Hexane	–11 nm	
Cyclohexane	–11 nm	

It has been found is most of the cases that the experimental λ_{max} values for α,β-unsaturated carbonyl compounds are same or near the same as those calculated on the basis of Table 4.4.

The method can be illustrated by the following three worked examples:

1.



Base value for α,β-unsaturated 6-ring ketone = 215 nm

Increments for: One β-ring residue = 12 nm

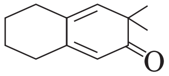
One γ-alkyl substituent and one δ-ring residue (2 × 17 nm) = 34 nm

One exocyclic double bond = 5 nm

One additional conjugation = 30 nm

$\therefore$ Calculated λ_{max} = 296 nm

2.



Base value for α,β-unsaturated 6-ring ketone = 215 nm

Increments for: One homodiene system = 39 nm

One β-ring residue = 12 nm

One γ-ring residue = 18 nm

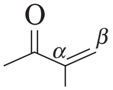
One δ-ring residue = 18 nm

Two exocyclic double bonds (2 × 5 nm) = 10 nm

One additional conjugation = 30 nm

$\therefore$ Calculated λ_{max} = 342 nm

3.



Base value for acyclic α, β-unsaturated ketone = 215 nm

Increment for one α-alkyl group = 10 nm

$\therefore$ Calculated λ_{max} = 225 nm

[**N.B.** Had the spectrum been recorded in water, λ_{max} would have moved to (225 + 8) = 233 nm.]

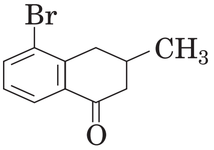
4.2.12 Rules for Calculating λ_{max} for $\pi \rightarrow \pi^*$ Transitions in Benzoyl Derivatives

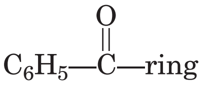
Scott devised a set of rules for calculating the absorption maximum for the derivatives of acyl benzenes. These rules which help us in estimating the λ_{max} in ethanol in a number of substituted aromatic ketones, aldehydes, acids and esters ($RC_6H_4{-}\underset{\underset{O}{\|}}{C}{-}X$, where X=H, R, OH or OR), are given in Table 4.5.

Table 4.5 Substituted aromatic ketones, aldehydes, acids and esters (in ethanol); λ_{max} for $\pi \rightarrow \pi^*$ transition

Base value for PhCHO	250 nm	
Base value for PhCOR (R may be a ring residue)	246 nm	
Base value for PhCOOH or PhCOOR	230 nm	
Increment for substituents:		
Alkyl or ring residue	*o*, *m*	3 nm
—OH or —OR	*p*	10 nm
	o, *m*	7 nm
	p	25 nm
$—O^{\ominus}$	*o*	11 nm
	m	20 nm
	p	78 nm
— Cl	*o*, *m*	0 nm
	p	10 nm
—Br	*o*, *m*	2 nm
	p	15 nm
$—NH_2$	*o*, *m*	13 nm
	p	58 nm
$—NHCOCH_3$	*o*, *m*	20 nm
	p	45 nm
$—NHCH_3$	*p*	73 nm
$—N(CH_3)_2$	*o*, *m*	20 nm
	p	85 nm

Following are two simple applications of these rules:

1. 

Base value for  $C_6H_5—\overset{\overset{\displaystyle O}{\|}}{C}—$ring residue = 246 nm

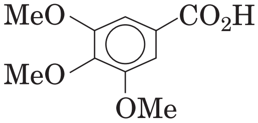
Increments for:

o-ring residue = 3 nm

m-Br = 2 nm

∴ Calculated λ_{max} = 251 nm

2.



Base value for $C_6H_5CO_2H$ = 230 nm

Increments for:

o- and *m*-OMe (2 × 7 nm) = 14 nm

p-OMe = 25 nm

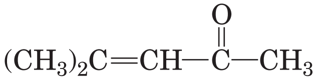
∴ Calculated λ_{max} = 269 nm

4.2.13 Applications of Ultraviolet Spectroscopy

Some important applications of ultraviolet spectroscopy are as follows:

(a) Detection of functional groups The technique can be applied to detect the presence or absence of a particular chromophore in the compound. The absence of a band at a particular wavelength may be regarded as an evidence for the absence of a particular group. If the spectrum is transparent above 200 nm, it shows the absence of (i) C═C—C═C, (ii) C═C—C═O or (iii) Ar—C═O moiety in the compound.

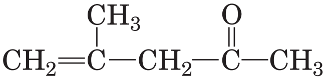
(b) Distinction between a conjugated and a nonconjugated compound A conjugated compound can be distinguished from a nonconjugated compound by UV spectroscopy. For example, compound I absorbs at nearly 239 nm, whereas the compound II is transparent above 200 nm.



$(CH_3)_2C{=}CH{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3$

I

(conjugated: λ_{max} ~ 239 nm)



$CH_2{=}\overset{\overset{\displaystyle CH_3}{|}}{C}{-}CH_2{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3$

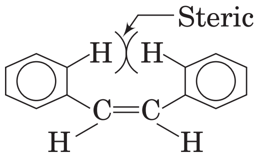
II

(non-conjugated)

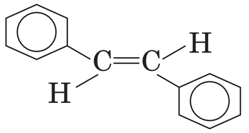
(c) Extent of conjugation The extent of conjugation in polyenes R—$(CH{=}CH)_n$—R can be estimated by UV spectroscopy,

(d) Identification of polynuclear hydrocarbons Benzene as well as polynuclear hydrocarbons have characteristic spectra in UV and visible region. Thus, they can be identified by comparing with known polynuclear compounds.

(e) Determination of configurations of geometrical isomers *cis*-Alkenes generally absorb at different wavelengths as compared to the isomeric *trans*-alkenes. Because of steric strain, the *cis*-alkene becomes nonplanar and consequently, absorption occurs at a lower wavelength compared to the *trans*-alkene. *cis*-Stilbene, for example absorbs at 283 nm, whereas *trans*-stilbene absorbs at 295.5 nm.

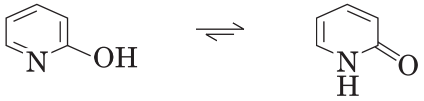


cis-Stilbene
(λ_{max} = 283 nm)



trans-Stilbene
(λ_{max} = 295.5 nm)

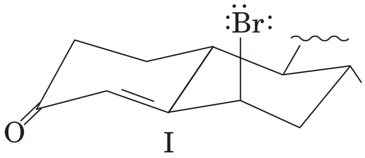
(f) Detection of the preference of a particular tautomeric form If a molecule exists in two tautomeric forms, preference of one over the other can be detected by UV spectroscopy. 2-Hydroxypyridine, for example, exists in equilibrium with its tautomeric form 2-pyridone.



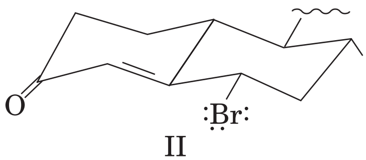
2-Hydroxypyridine 2-Pyridone

The spectra of these two compounds were found to favour 2-pyridone which contains a C=C—C=O moiety. The equilibrium is, therefore, shifted towards the right.

(g) Distinction between equatorial and axial conformations UV spectroscopic technique can also be used to distinguish between equatorial and axial conformations. The $n \rightarrow \pi^*$ (R-bond) transition which appears at longer wavelength in α,β-unsaturated ketones is influenced by a polar group in the γ-position. An axial γ-substituent shifts the absorption to longer wavelength compared to an equatorial γ-substituent. The compound I, for example, absorbs at a longer wavelength compared to the compound II. Thus, the two diastereoisomeric compounds can be distinguished by comparing their λ_{max} values.



I



II

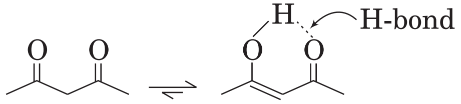
(h) Determination of the strength of H-bond Protic solvents form H-bonds with the n-electrons of carbonyl oxygen. Because of this, the energy of n-electrons in the ground state is decreased depending upon the strength of H-bond. The $n \rightarrow \pi^*$ transition is, therefore, shifted towards the shorter wavelength. Hence, by measuring the λ_{max} of a carbonyl compound in a nonpolar and protic polar solvent, the strength of H-bond can be determined.

(i) Distinction between aromatic and aliphatic amines Aromatic amines can be distinguished from aliphatic amines by comparing the spectral pattern of the neutral solution with that of the acidic solution. Aromatic amines show a significant hypsochromic shift (blue shift), while aliphatic amines do not.

(j) Distinction between phenols and alcohols Phenols can be distinguished from alcohols by comparing the spectral pattern of the neutral with that of the alkaline solution. Phenolic compounds show a bathochromic shift (red shift), while alcohols show no appreciable change in the spectral pattern by increasing the pH of the medium.

(k) Distinction between *β*- and *γ*-diketones *β*-Diketones remain mainly in the enol form which are conjugated systems exhibiting characteristic absorption band at a longer wavelengths. The enol forms of *γ*-diketones are not at all conjugated and so they exhibit no characteristic absorption band. Thus, they can be distinguished by comparing their spectral pattern.

Pentane-2,4-dione:
(a *β*-diketone)



(keto-form) (enol-form)

SOLVED PROBLEMS

1. **(a) What percent of incident radiation is transmitted by a sample when its absorbance is 1.0 and 0, respectively?**
   (b) What is the absorbance of a sample that transmits one-half of the incident radiation?

Solution

(a) $A = \log I_0/I$

or $1 = \log I_0/I$

or $\log 10 = \log I_0/I$

or $10 = I_0/I$

or $I = I_0/10$, i.e., 10% of the incident radiation is transmitted.

Again, $0 = \log I_0/I$

or $\log 1 = \log I_0/I$

or $1 = I_0/I$

or $I = I_0$, i.e., 100% of the incident radiation is transmitted.

(b) $A = \log I_0/I = \log \dfrac{1}{1/2} = \log 2 = 0.3010$

2. **A 4×10^{-5} M solution of isoprene (2-methyl-1,3-butadiene) in a 1.0-cm cell at λ_{max} = 222 nm has an A = 0.8. Calculate ε_{max} for this transition.**

Solution

$$\varepsilon_{\max} = A/cl = 0.8/(4 \times 10^{-5}\ \text{mol l}^{-1})(1.0\ \text{cm}) = 2 \times 10^{4}\ \text{l mol}^{-1}\ \text{cm}^{-1}$$

3. **A 9.37×10^{-5} M solution of a compound in a 1.0-cm cell at $\lambda_{\max}$ = 235 nm has an A = 1.18. Calculate the concentration of the compound if its absorbance A = 0.96 at $\lambda_{\max}$.**

Solution

$$\varepsilon_{\max} = A/cl = 1.18/(9.37 \times 10^{-5}\ \text{mol l}^{-})(1.0\ \text{cm}) = 1.26 \times 10^{4}\ \text{l mol}^{-1}\ \text{cm}^{-1}$$

The molar absorptivity (ε) is a constant for a particular compound at a given wavelength. Therefore, the concentration of the compound if its absorbance A = 0.96 at $\lambda_{\max}$ is:

$$c = A/\varepsilon l = 0.96/(1.26 \times 10^{4}\ l\ \text{mol}^{-1}\ \text{cm}^{-1})(1.0\ \text{cm}) = 7.6 \times 10^{-5}\ \text{mol}\ l^{-1}$$

4. **A compound (molecular mass 110) has an absorption band with $\lambda_{\max}$ = 215 nm (ε = 10,000). A solution of this compound shows absorbance A = 2.0 with a 1-cm cell. Calculate the concentration of this compound in this solution in grams per litre.**

Solution $A = \varepsilon cl$

or $c = A/\varepsilon l = 2.0/10^{4} \times 1 = 2 \times 10^{-4}\ \text{mol}\ l^{-1}$

or $c = 2 \times 10^{-4} \times 110$ or $2.2 \times 10^{-2}\ \text{gl}^{-1}$

5. **In UV-VIS spectrum, absorption bands appear rather than absorption lines. Account for this observation.**

Solution Each electronic energy level is associated with its vibrational and rotational energy levels. Thus, electron transitions may occur from any of several vibrational and rotational states of an electronic level to any of the several vibrational and rotational state of a higher level and as a result of this, most absorption bands in the visible and ultraviolet region are broad.

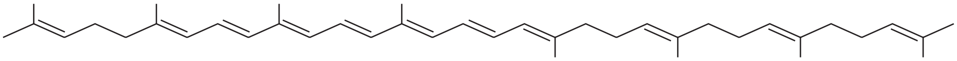
6. **Account for the following observations:**
   - **(a) Ethylene is colourless, but the polyene $CH_3(CH{=}CH)_6CH_3$ is yellow.**
   - **(b) Most free radicals are coloured.**
   - **(c) Lycopene, which contributes to the colour of ripe tomatoes, is a red substance.**
   - **(d) β-Carotene, which is responsible for the colour of carrots, is an orange substance.**
   - **(e) 1,4-Pentadiene does not absorb light above 200 nm.**
   - **(f) The absorption of nitrobenzene is more intense than benzene and the wavelength is shifted to longer region.**
   - **(g) $\sigma \rightarrow \pi^*$ and $\pi \rightarrow \sigma^*$ electronic transitions do not take place.**

Solution

(a) Ethylene has $\lambda_{\max}$ = 175 nm and $\varepsilon_{\max}$ = 5000. This absorption band is due to $\pi \rightarrow \pi^*$ transition, and since it is in the far UV region, ethylene is coloureless. As conjugation increases, the energy difference between HOMO and LUMO decreases (the energy of HOMO increases and the energy of LUMO decreases) and when it reaches the visible region, colour (complementary) appears in the compound. In the highly conjugated polyene $CH_3(CH{=}CH)_6CH_3$, the HOMO—LUMO energy gap is quite small. So, the absorption occurs in the blue region and consequently, the compound appears yellow (the complementary colour).

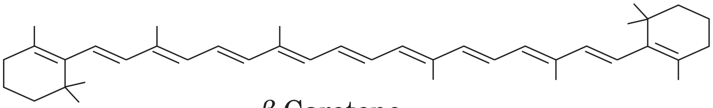
(b) The presence of the unpaired electron in a free radical changes the electronic energy levels from those in the parent molecule. In general, the energy difference between the highest occupied and lowest unoccupied MOs is lowered, and consequently, the absorption wavelength is lengthened and may enter the visible region. Because of this, most free radicals are coloured.

(c) Lycopene is a highly conjugated system of 11 double bonds and absorbs in the blue region of visible light (λ_{max} = 505 nm). Because of this, lycopene appears red.



Lycopene
(red)

(d) Since *β*-carotene contains a large number (eleven) of conjugated double bonds, it has an absorption maximum at 497 nm, well into the visible region. Thus, when a sample of *β*-carotene is exposed to white light, blue-green light is absorbed, and eye perceives the complementary colour of blue-green, which is red-orange.



β-Carotene
(red-orange)

(e) 1,4-Pentadiene ($CH_2{=}CHCH_2CH{=}CH_2$) is a nonconjugated diene. Because of this, its HOMO–LUMO energy gap is much larger and so, it does not absorb light above 200 nm.

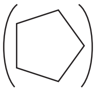
(f) Benzene is a symmetrical molecule and consequently, has no transition dipole. However, since some bending vibrations distort its shape, benzene does show absorption. Introduction of substituents into the benzene ring destroys its symmetry and thereby gives rise to an increased intensity of absorption, and by extending the conjugation, increases the wavelength of the absorption band. Thus, since nitrobenzene ($PhNO_2$) has a large transition dipole, its absorption is more intense than that of benzene, and because of extended conjugation, the wavelength is shifted to the longer region (red shift).

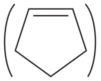
(g) If the axis of the unoccupied orbital remains oriented along the nodal plane of the occupied orbital, no electronic transition takes place. The axis of the *σ*-bond remains oriented along the nodal plane of *p*-orbital which forms *π*-bond. Again, the axis of *p* orbital remains oriented along the nodal plane of the orbital forming σ-bond. Because of this, $\pi \rightarrow \sigma^*$ and $\sigma \rightarrow \pi^*$ transitions are symmetry forbidden, i.e., these types of electronic transitions do not take place at all.

7. **What type of electronic transitions do you except from each of the following compounds?**
   (a) Ethane, (b) Cyclopentane, (c) Cyclopentene, (d) Methanol, (e) Propanal, (f) Vinyl chloride

Solution

(a) Ethane (CH_3—CH_3) contains only σ (bonding) MO's. Therefore, only $\sigma \rightarrow \sigma^*$ electronic transition is expected to take place in ethane.

(b) Cyclopentane  also contains σ(bonding) MO's. So the only electronic transition one would expect is $\sigma \rightarrow \sigma^*$.

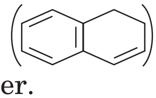
(c) Cyclopentene  contains σ and π MO's. Therefore, $\sigma \rightarrow \sigma^*$ and $\pi \rightarrow \pi^*$ electronic transitions are expected to take place in this compound.

(d) Methanol ($CH_3\ddot{\underset{\cdot\cdot}{O}}H$) contains σ and n MO's. Therefore, $\sigma \rightarrow \sigma^*$ and $n \rightarrow \sigma^*$ electronic transitions are expected to take place in this compound.

(e) Propanal ($CH_3CH_2CH{=}\ddot{O}{:}$) contains σ, π and n MO's. Therefore the expected electronic transitions are: $\sigma \rightarrow \sigma^*$, $n \rightarrow \sigma^*$, $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$.

(f) Vinyl chloride ($CH_2{=}CH{-}\ddot{\underset{\cdot\cdot}{C}}l{:}$) also contains σ, π and n MO's. So, also in this case, the expected electronic transitions are: $\sigma \rightarrow \sigma^*$, $n \rightarrow \sigma^*$, $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$.

8. **Which member of each pair absorbs UV/VIS light at a longer wavelength than the other?**
   (a) 1,3-Pentadiene and 1,4-pentadiene
   (b) Hept-1-en-4-one and hept-2-en-4-one
   (c) Propiophenone and phenylacetone
   (d) 1,2-Dihydronaphthalene and 1,4-dihydronaphthalene

Solution Conjugated dienes and enones have longer wavelengths of absorptions than do nonconjugated. Therefore, (a) 1,3-pentadiene ($CH_2{=}CH{-}CH{=}CHCH_3$), (b) hept-2-en-4-one ($CH_3CH_2CH_2COCH{=}CHCH_3$), (c) propiophenone ($PhCOCH_2CH_3$) and (d) 1,2-dihydronaphthalene  will absorb UV/VIS light at longer wavelengths compared to the other member.

9. **(a) Account for the following variations in λ_{max} of CH_3Cl (173 nm), CH_3Br (204 nm), and CH_3I (258 nm).**
   (b) Explain the following λ_{max} (nm) values given in parentheses: methane (125); ethane (185); cyclopropane (190)

Solution

(a) The electronic transition must be $n \rightarrow \sigma^*$. On going from Cl to Br to I, the n electrons (i) are found in higher principal energy levels (3, 4 and 5, respectively), (ii) are progressively less tightly held with the nucleus and (iii) are more easily excited. Therefore, absorption occurs at progressively higher λ_{max} since less energy is progressively required.

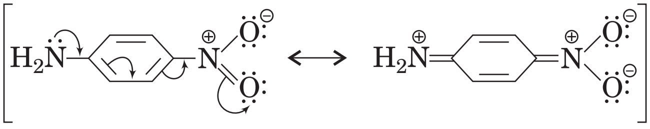
(b) Since these compounds contain only single bonds, absorption must be due to $\sigma \rightarrow \sigma^*$ transitions. In methane (CH_4), the only transition possible is that of the C—H bond. In ethane (CH_3—CH_3), transitions for the C—H and C—C bonds are possible. The latter transition requires less energy to bring it about and so, this occurs at a longer wavelength compared to that for the C—H bond. Therefore, the absorption band at 185 nm is due to the transition involving the C—C bond in ethane. Cyclopropane (Δ) can also undergo only $\sigma \rightarrow \sigma^*$ transitions involving C—C and C—H bonds. The absorption band at 190 nm is due to the transition involving the C—C bond. However, the C—C bonds in cyclopropane are not 'pure' σ bonds. They possess certain amount of π bond character (π bonds are p—p bonds). Hence, because of partial π bond character of the C—C bonds, the energy required for $\sigma \rightarrow \sigma^*$ transition is less than that required in the case of 'pure' σ bond as in ethane and as a consequence, the λ_{max} of cyclopropane is shifted to a longer wavelength.

10. (a) For disubstituted benzene derivatives predict the relative red shifts when electron-donating and electron-withdrawing groups are (i) *para*, (ii) *ortho* and (iii) *meta* to each other.

(b) Predict the effect of two electron-releasing or electron-withdrawing groups in the same ring.

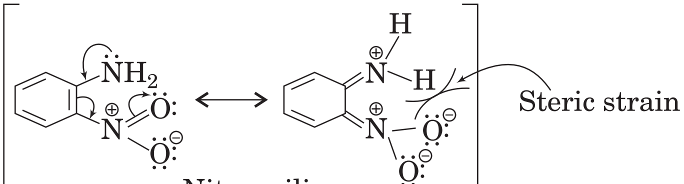
Solution

(a) (i) When electronically complementary groups such as amino and nitro, are situated *para* to each other as in *p*-nitroaniline, there is pronounced red shift (in the main absorption band) which is much greater than the sum of the individual effects of the two substituents due to the extension of the chromophore from the electron-donating to the electron-withdrawing substituent through the benzene ring.



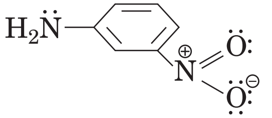
p-Nitroaniline

(ii) When the two complementary groups are situated *ortho* to each other, the red shift is a little greater than the sum of the individual effect of the two substituents because steric strain caused by these two adjacent groups hampers the coplanarity of the system needed to achieve resonance interaction.



o-Nitroaniline

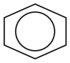
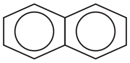
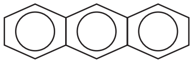
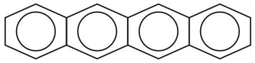
(iii) When the two complementary groups are situated *meta* to each other as in *m*-nitroaniline, there is no interaction between the two groups (due to lack of conjugation) and the magnitude of the shift is approximately equal to the sum of the individual shifts.



(*m*-nitroaniline)

(b) The effect of two electronically similar groups are not additive. So, the effect of two such groups in the same ring is similar to those for monosubstituted benzenes.

11.

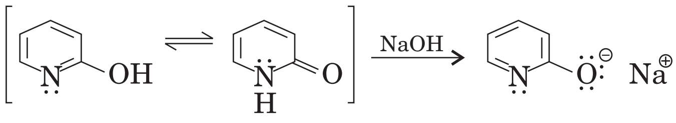
	Benzene	Naphthalene	Anthracene	Naphthacene
λ_{max}:	254 nm	314 nm	380 nm	480 nm

As the number of linearly fused benzene rings increases, λ_{max} of the benzenoid band shifts towards longer wavelength. Explain this observation.

Solution The HOMO–LUMO energy gap of aromatic benzene molecule is considerably high because transfer of an electron from HOMO to LUMO causes destruction of aromatic sextet of aromatic stability of the molecule. As the number of linearly fused benzene rings increases, the degree of aromatic stability decreases and the degree of conjugation increases. As a result, the HOMO–LUMO energy gap decreases and consequently, the λ_{max} shifts to longer wavelength.

12. The λ_{max} of neutral or acidic solution of 2-hydroxypyridine is higher than that of its alkaline solution. Explain.

Solution

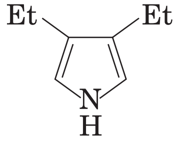


I II III

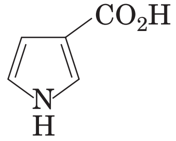
2-Hydroxypyridine

In neutral or acidic solution, 2-hydroxypyridine mainly exists in the amide form II. It is nonaromatic and the conjugation in it is extended. Because of this, the HOMO–LUMO energy gap is small and the compound absorbs at a longer wavelength. When the compound is treated with a base, it becomes converted to III. Since the structure III is aromatic, the HOMO–LUMO energy gap is large and the compound absorbs at a shorter wavelength.

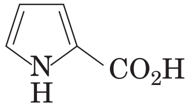
13. Explain why the λ_{max} value increases on going from I to III.



I



II

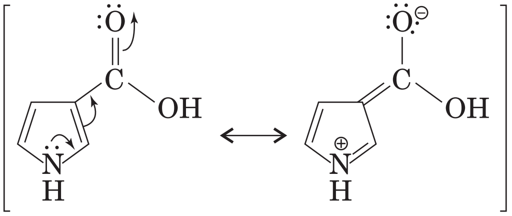


III

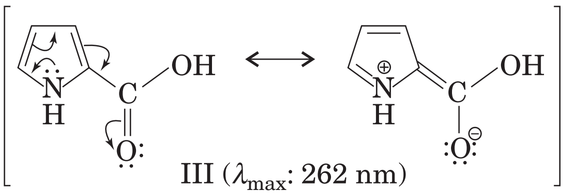
λ_{max}: 203 nm 245 nm 262 nm

Solution The conjugation in II from nitrogen lone pair through the pyrrole ring (involving one double bond) to the carbonyl group at C-3 increases the length of the chromophore and because of this, absorption occurs at a wavelength longer than I in which there is no extended conjugation.

The conjugation in III from nitrogen lone pair through the pyrrole ring (involving two double bonds) to the carbonyl group at C-2 further increases the length of the chromophore and because of this, absorption occurs at a wavelength longer than II.



II (λ_{max}: 245 nm)



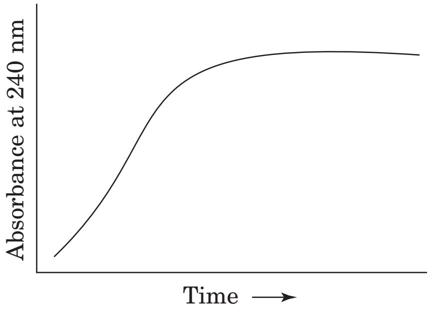
III (λ_{max}: 262 nm)

14. How can the rate of a reaction be measured using UV spectroscopy? Give an example.

Solution To measure the rate of a reaction by UV-VIS spectroscopy one of the reactants or one of the products must have a distinct observable absorption at which other reactants and products have little or no absorbance. The UV spectrophotometer is adjusted to measure the absorbance, A, of either the product or the reactant at its λ_{max} as a function of time instead of absorbance as a function of wavelength and the rate of the reaction is determined by monitoring the increase or decrease in absorbance with time at that λ_{max}. The rate of the following reaction, for example, can be measured by UV-VIS spectroscopy.

$$\underset{\text{Nitromethane}}{CH_3NO_2} + OH^{\ominus} \rightleftharpoons \underset{\substack{\text{Nitromethyl anion}\\ (\lambda_{max} = 240\text{ nm})}}{\overset{\ominus}{C}H_2NO_2} + H_2O$$

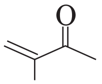
The anion of nitromethane has a λ_{max} = 240 nm, but either H_2O or the reactants do not show any significant absorbance at that wavelength. In order to measure the rate at which the nitromethyl anion is formed, i.e., the rate at which $OH^{\ominus}$ takes up a proton from nitromethane, the UV spectrophotometer is adjusted to measure absorbance at 240 nm as a function of time. Nitromethane is added to a quartz cell containing an alkali solution, and the rate of the reaction is determined by monitoring the increase in absorbance with time at 240 nm.



15. How can the rates of the following reactions be determined by UV spectroscopy?

(a) $CH_2{=}CH{-}CH{=}CH_2 + H_2\ (1\ \text{equiv.}) \longrightarrow$

(b)



$\xrightarrow[\text{2. } H_3O^{\oplus}]{\text{1. } (Me_2CHO)_3Al \text{ in } Me_2CHOH \text{ (MPV)}}$

(c) $C_6H_5CH_2CH_2OH \xrightarrow[\Delta]{H^{\oplus}}$

Solution

(a) Either 1,2- or 1,4-addition converts a conjugated diene to a simple alkene ($CH_3CH_2CH{=}CH_2$ or $CH_3CH{=}CHCH_3$), 1,3-Butadiene absorbs at 217 nm. Therefore, the rate of hydrogenation can be determined by monitoring the decrease in absorbance at 217 nm with time.

(b) MPV reduction converts the α, β-unsaturated ketone (λ_{max} = 225 nm) to an unsaturated alcohol ($CH_2{=}CMeCHOHMe$). Therefore, the rate of the reaction can be determined by monitoring the decrease in absorbance at 225 nm with time.

(c) 2-Phenylethanol undergoes acid-catalyzed dehydration to give styrene ($C_6H_5CH{=}CH_2$). Benzene has two important absorptions: K-band and B-band. Both of these shift to longer wavelength (204–248 nm and 254–282 nm). Therefore, the rate of the reaction can be determined by monotoring the increase in absorbance at either 248 or 282 nm with time.

16. Mesityl oxide ($Me_2C = CHCOMe$) shows two absorption bands one at 230 nm and another at 321 nm in isooctane. Assign these λ_{max} values in terms of electronic transitions. How do these absorption bands change their positions on changing the solvent from isooctane to water?

Solution The $\pi \rightarrow \pi^*$ transition corresponds to the absorption band at 230 nm, whereas $n \rightarrow \pi^*$ transition corresponds to the absorption band at 321 nm.

On increasing the polarity of the solvent (isooctane to water) the $\pi \rightarrow \pi^*$ absorption band moves to longer wage-length (red shift), whereas $n \rightarrow \pi^*$ absorption band moves to shorter wavelength (blue shift).

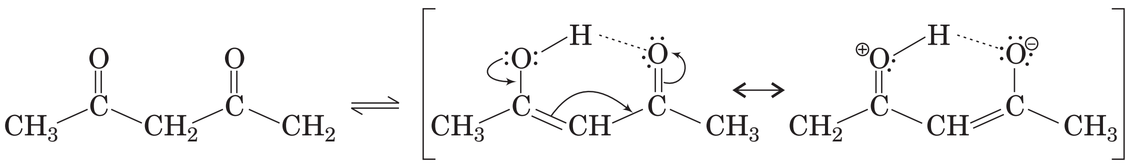
17. The absorption spectra of 4-methylpent-3-en-2-one gives two sets of λ_{max} values: (i) 230 nm and 321 nm and (ii) 237.6 nm and 314 nm in two different solvents. Identify the bands and name the solvent (chloroform or petroleum ether) associated with each set of λ_{max} values.

Solution The lower λ_{max} values (230 and 237.6 nm) are due to $\pi \rightarrow \pi^*$ transitions (K-band) and the higher λ_{max} values (321 and 314 nm) are due to $n \rightarrow \pi^*$ transitions (R-band).

Since the lower value, i.e., the $\pi \rightarrow \pi^*$ transition, is increased (230 → 237.6 nm) and the higher value, i.e., the $n \rightarrow \pi^*$ transition is decreased (321 → 314 nm) on going from 1st to the 2nd set, petroleum ether (a nonpolar solvent) is associated with the 1st set of λ_{max} values and chloroform (a polar solvent) is associated with the 2nd set of λ_{max} values.

18. In aqueous solution acetylacetone shows an UV absorption band at λ_{max} = 274 nm (ε_{max} = 2,050). Explain why the intensity is increased markedly when the spectrum is recorded in isooctane (λ_{max} = 272, ε_{max} = 12,000).

Solution Acetylacetone ($CH_3COCH_2COCH_3$) exists as an equilibrium mixture of two tautomeric forms:



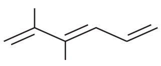
Keto-form
(more polar)

Enol-form
(less polar)

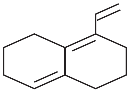
It is the enol tautomer which is responsible for the absorption of acetylacetone and therefore, the intensity of absorption depends on the concentration of the enol tautomer. The keto tautomer is more polar than the enol tautomer. So, in highly polar solvent water, the keto tautomer exists predominantly. On the other hand, the less polar enol tautomer exists predominantly in the nonpolar solvent isooctane. For this reason, the absorption band of acetylacetone becomes more intense when the solvent is changed from water to isooctane.

19. Use Woodward-Fieser rules to calculate the λ_{max} values for the $\pi \rightarrow \pi^*$ transition in the following compounds (in ethanol):

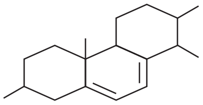
(a)



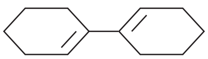
(b)



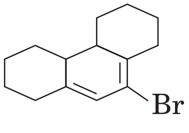
(c)



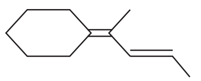
(d)



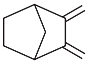
(e)



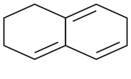
(f)



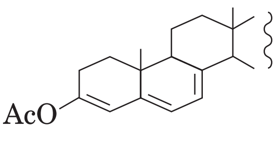
(g)



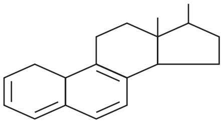
(h)



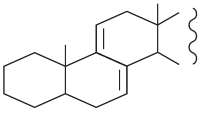
(i)



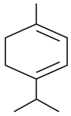
(j)



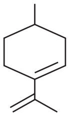
(k)



(l)

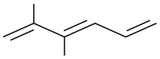


(m)



Solution

(a)



It is an acyclic diene with two alkyl substituents and one double bond which extends conjugation.

Base value = 215 nm

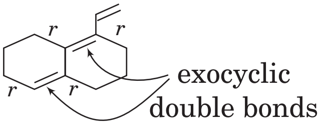
Increments for:

Two alkyl substituents (2 × 5 nm) = 10 nm

One conjugated C═C = 30 nm

∴ Calculated λ_{max} = 255 nm

(b)



It is a heteroannular diene with two exocyclic double bond, four ring residues and one double bond that extends conjugation.

Base value = 215 nm

Increments for:

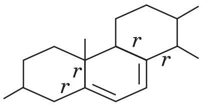
Four ring residues (4 × 5 nm) = 20 nm

Two exocyclic double bonds (2 × 5 nm) = 10 nm

One conjugated C═C = 30 nm

∴ Calculated λ_{max} = 275 nm

(c)



It is a homoannular diene with four ring residues and two exocyclic double bonds.

Base value = 253 nm

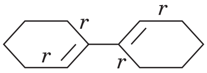
Increments for:

Four ring residues (4 × 5 nm) = 20 nm

Two exocyclic double bonds (2 × 5 nm) = 10 nm

∴ Calculated λ_{max} = 283 nm

(d)



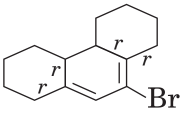
It is a heteroannular diene with four ring residues.

Base value = 215 nm

Increment for:

Four ring residues (4 × 5 nm) = 20 nm

∴ Calculated λ_{max} = 235 nm

(e) 

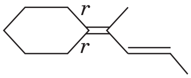
It is a homoannular diene with four ring residues and two exocyclic double bonds.

Base value = 253 nm

Increments for:

Four ring residues (4 × 5 nm) = 20 nm
One –Br substituent = 5 nm
Two exocyclic double bonds (2 × 5 nm) = 10 nm

∴ Calculated λ_{max} = 288 nm

(f) 

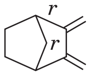
It is an acyclic diene with two alkyl substituents, two ring residues and one exocyclic double bond.

Base value = 215 nm

Increments for:

Two alkyl substituents (2 × 5 nm) = 10 nm
Two ring residues (2 × 5 nm) = 10 nm
One exocyclic double bond = 5 nm

∴ Calculated λ_{max} = 240 nm

(g) 

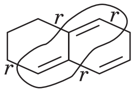
It is a bicyclic diene with two ring residues and two exocyclic double bonds.

Base value = 215 nm

Increments for:

Two ring residues (2 × 5 nm) = 10 nm
Two exocyclic double bonds (2 × 5 nm) = 10 nm
Strain correction for one bicyclic system = 15 nm

∴ Calculated λ_{max} = 250 nm

(h) 

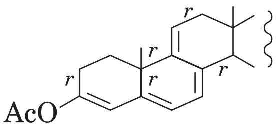
It is a heteroannular diene with four ring residues and two exocyclic double bonds. Due to cross conjugation, the third double bond, contributes nil.

Base value = 215 nm

Increments for:

Four ring residues (4 × 5 nm) = 20 nm
Two exocyclic double bonds (2 × 5 nm) = 10 nm

∴ Calculated λ_{max} = 245 nm

(i) 

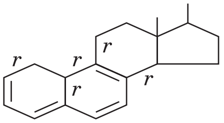
It is a homoannular diene with five ring residues, three exocyclic double bonds, one —OAc substituent and two double bonds which extend conjugation.

Base value = 253 nm

Increments for:

Five ring residues (5 × 5 nm) = 25 nm
Three exocyclic double bonds (3 × 5 nm) = 15 nm
One —OAC substituent = 0 nm
Two conjugated C═C (2 × 30 nm) = 60 nm

∴ Calculated λ_{max} = 353 nm

(j) 

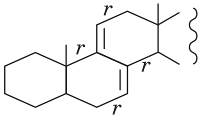
It is a homoannular diene with five ring residues, one exocyclic double bond and two double bonds which extend conjugation.

Base value = 253 nm

Increments for:

Five ring residues (5 × 5 nm) = 25 nm
One exocyclic double bond = 5 nm
Two conjugated C═C (2 × 30 nm) = 60 nm

∴ Calculated λ_{max} = 343 nm

(k) 

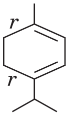
It is a heteroannular diene with four ring residues and two exocyclic double bonds.

Base value = 215 nm

Increments for:

Four ring residues (4 × 5 nm) = 20 nm
Two exocyclic double bonds (2 × 5 nm) = 10 nm

∴ Calculated λ_{max} = 245 nm

(l) 

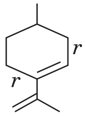
It is a homoannular diene with two ring residues and two alkyl substituents.

Base value = 253 nm

Increments for:

Two ring residues (2 × 5 nm) = 10 nm
Two alkyl substituents (2 × 5 nm) = 10 nm

∴ Calculated λ_{max} = 273 nm

(m) 

It is a heteroannular diene with two ring residues and one alkyl substituent.

Base value = 215 nm

Increments for:

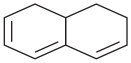
Two ring residues (2 × 5 nm) = 10 nm

One alkyl substituent = 5 nm

∴ Calculated λ_{max} = 230 nm

[It is to be noted that the calculated λ_{max} values are nearly equal to or equal to the observed values.]

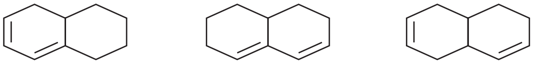
20. Catalytic hydrogenation of the triene A with one equivalent of H_2 give three isomeric dienes B, C and D.



$$(A) \xrightarrow[\text{Pt}]{H_2 \text{ (1 equiv.)}} B + C + D$$

How can you identify the resulting dienes by calculating λ_{max} values using Woodward–Fieser rules?

Solution The structures of the three isomeric dienes are as follows:



For the diene B:

Base value = 253 nm

Increments for:

Three ring residues (3 × 5 nm) = 15 nm

One exocyclic double bond = 5 nm

∴ Calculated λ_{max} = 273 nm

For the diene C:

Base value = 215 nm

Increments for:

Three ring residues (3 × 5 nm) = 15 nm

One exocyclic double bond = 5 nm

∴ Calculated λ_{max} = 235 nm

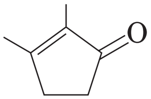
For the diene D:

As this diene is not a conjugated one, its λ_{max} value will be less than 200 nm, i.e., it will be trasparent above 200 nm.

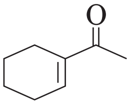
Therefore, the three dienes can be distinguished by their expected λ_{max} values.

21. Calculate the λ_{max} values for the $\pi \rightarrow \pi^*$ transition in the following compounds (in ethanol) by using Woodward–Fieser rules.

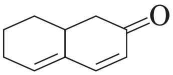
(a)



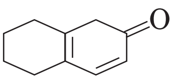
(b)



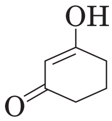
(c)



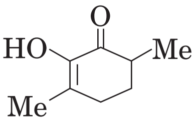
(d)



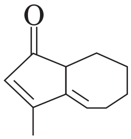
(e)



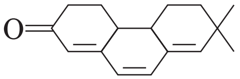
(f)



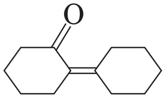
(g)



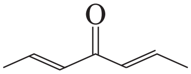
(h)



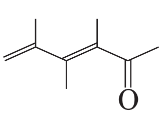
(i)



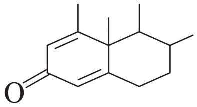
(j)



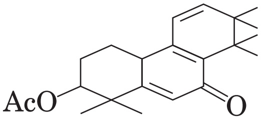
(k)



(l)

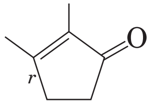


(m)



Solution

(a)



It is an α,β-unsaturated five-ring ketone with one α-alkyl substituent, one β-alkyl substituent and one β-ring residue.

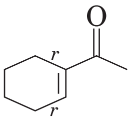
Base value = 202 nm

Increment for:

One α-alkyl substituent = 10 nm
One β-alkyl substituent = 12 nm
One β-ring residue = 12 nm

$\therefore$ Calculated λ_{max} = 236 nm

(b)



It is an α,β-unsaturated acyclic ketone with one α- and one β-ring residue.

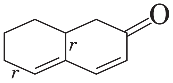
Base value = 215 nm

Increment for:

One α-ring residue = 10 nm
One β-ring residue = 12 nm

$\therefore$ Calculated λ_{max} = 237 nm

(c)



It is an α,β-unsaturated 6-ring ketone with one γ-ring residue, one δ-ring residue, one additional conjugation and one exocyclic double bond.

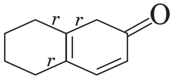
Base value = 215 nm

Increments for:

One γ-ring residue = 18 nm
One δ-ring residue = 18 nm
One additional conjugation = 30 nm
One exocyclic double bond = 5 nm

∴ Calculated λ_{max} = 286 nm

(d)



It is an α,β-unsaturated six-ring ketone with one γ-ring residue, two δ-ring residues and one additional conjugation. Also, it contains a homodiene system.

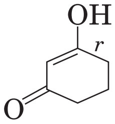
Base value = 215 nm

Increments for:

One homodiene system = 39 nm
One γ-ring residue = 18 nm
Two δ-ring residues (2×18 nm) = 36 nm
One additional conjugation = 30 nm

∴ Calculated λ_{max} = 338 nm

(e)



It is an α,β-unsaturated six-ring ketone system (actually the enol-form of a β-diketone) with one β-OH group and one β-ring residue.

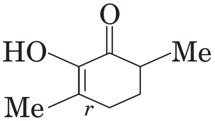
Base value = 215 nm

Increments for:

One β-OH group = 30 nm
One β-ring residue = 12 nm

∴ Calculated λ_{max} = 257 nm

(f)



It is an α, β-unsaturated 6-ring ketone system (actually the enol form of a α-diketone) with one α-OH group, one β-alkyl alkyl substituent and one β-ring residue.

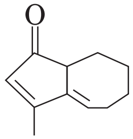
Base value = 215 nm

Increments for:

One α-OH group = 35 nm
One β-alkyl group = 12 nm
One β-ring residue = 12 nm

$\therefore$ Calculated $\lambda_{\max}$ = 274 nm

(g)



It is an α,β-unsaturated five-ring ketone with one β-alkyl substituent, one γ-ring residue, one δ-ring residue, one additional conjugation and one exocyclic double bond.

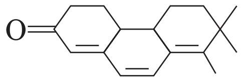
Base value = 202 nm

Increments for:

One β-alkyl substituent = 12 nm
One γ-ring residue = 18 nm
One δ-ring residue = 18 nm
One additional conjugation = 30 nm
One exocyclic double bond = 5 nm

$\therefore$ Calculated $\lambda_{\max}$ = 285 nm

(h)



It is an α,β-unsaturated six-ring ketone with one β-ring residue, two ω-ring residues, one ω-alkyl group, two exocyclic double bonds and two additional conjugated double bonds.

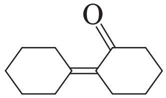
Base value = 215 nm

Increments for:

One β-ring residue = 12 nm
Two ω-ring residues (2 × 18 nm) = 36 nm
One ω-alkyl substituent = 18 nm
Two exocyclic double bonds (2 × 5 nm) = 10 nm
Two additional conjugated double bonds (2 × 30 nm) = 60 nm

$\therefore$ Calculated $\lambda_{\max}$ = 351 nm

(i)



It is an α, β-unsaturated six-ring ketone with one α-ring residue, two β-ring residues and one double bond exocyclic to both the rings.

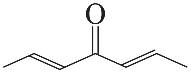
Base value = 215 nm

Increments for:

One α-ring residue = 10 nm
Two β-ring residues (2×12 nm) = 24 nm
One double bond exocyclic to both the rings = 10 nm

∴ Calculated λ_{max} = 259 nm

(j)



It is an acyclic α,β-unsaturated ketone with one β-alkyl substituent. Since the other double bond is cross-conjugated with the chromophore, it has no contribution to λ_{max}.

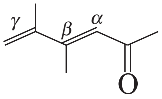
Base value = 215 nm

Increment for:

One β-alkyl substituent = 12 nm

∴ Calculated λ_{max} = 227 nm

(k)



It is an acyclic α,β-unsaturated ketone with one β-alkyl substituent, one γ-alkyl substituent and one additional conjugation.

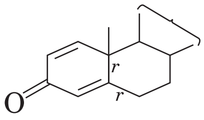
Base value = 215 nm

Increments for:

One β-alkyl substituent = 12 nm
One γ-alkyl substituent = 18 nm
One additional conjugation = 30 nm

∴ Calculated λ_{max} = 275 nm

(l)



It is an α,β-unsaturated six-ring ketone. There is a cross conjugation in this compound, i.e., the carbonyl group has α,β-unsaturation on either side. However, the value of λ_{max} is to be calculated by considering the most highly substituted conjugated system, i.e., the system containing the double bond exocyclic to the other ring.

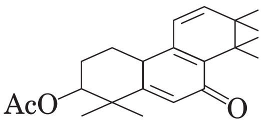
Base value = 215 nm

Increments for:

Two β-ring residues (2×12 nm) = 24 nm
One exocyclic double bond = 5 nm

∴ Calculated λ_{max} = 244 nm

(m)



It is an α,β-unsaturated six-ring ketone with one α-, one β- and one-γ-ring residue. Also, there is one additional conjugation and a homodiene system in the compound.

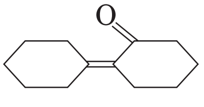
Base value = 215 nm

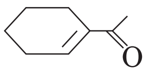
Increments for:

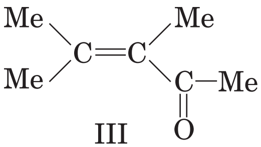
One α-ring residue = 10 nm
One β-ring residue = 12 nm
One δ-ring residue = 18 nm
One additional conjugation = 30 nm
One homodiene system = 39 nm

∴ Calculated $\lambda_{\max}$ = 324 nm

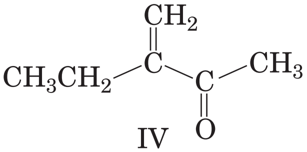
22. The following four ketones are kept in four bottles and their labels are removed. Their observed $\lambda_{\max}$ values are 221, 249, 237 and 258 nm. Assign structures to the appropriate $\lambda_{\max}$.


I


II



III



IV

Solution The $\lambda_{\max}$ values of these four α,β-unsaturated ketones are calculated by using Woodward-Fieser rules as follows:

For compound I:

Base value = 215 nm
One α-ring residue = 10 nm
Two β-ring residues (2×12 nm) = 24 nm
One double bond exocyclic to two rings = 10 nm

∴ Calculated $\lambda_{\max}$ = 259 nm

For compound II:

Base value = 215 nm
On α-ring residue = 10 nm
On β-ring residue = 12 nm

∴ Calculated $\lambda_{\max}$ = 237 nm

For compound III:

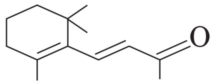
Base value = 215 nm
On α-alkyl group = 10 nm
Two β-alkyl substituents (2×12 nm) = 24 nm
∴ Calculated λ_{max} = 249 nm

For compound IV:

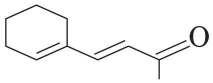
Base value = 215 nm
On α-alkyl substituent = 10 nm
∴ Calculated λ_{max} = 225 nm

Therefore, the compounds showing λ_{max} at 221, 249, 237 and 258 nm are IV, III, II and I, respectively. The observed values are nearly equal to or identical with the calculated values.

23. How can the UV spectral data λ_{max} 296 nm, ε_{max} 10,700 and λ_{max} 281 nm, ε_{max} 20800 be helpful in distinguishing the structures given below:



I

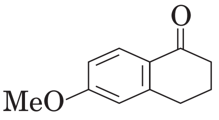


II

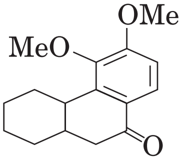
Solution The compound with λ_{max} 296 nm, ε_{max} 10700 has almost the half intensity of this band (K-band) as compared to the other. This decrease in intensity is due to steric strain caused by a methyl group and its effect on the absorption of the conjugated system. Therefore, the compound with decreased intensity of the K-band is I.

24. Calculate the absorption maximum in ethanol for each of the following compounds:

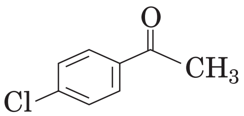
(a)



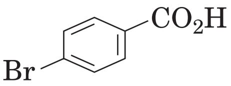
(b)



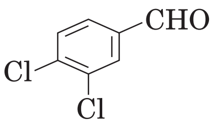
(c)



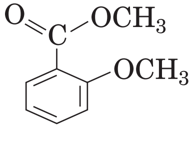
(d)



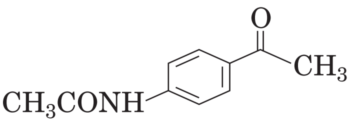
(e)



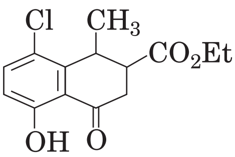
(f)



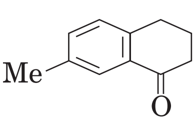
(g)



(h)

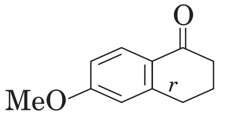


(i)



Solution

(a)



Base value for aromatic ketone = 246 nm

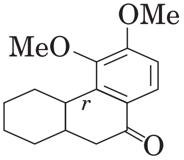
Increments for:

o-ring residue = 3 nm

p-OMe group = 25 nm

∴ Calculated λ_{max} = 274 nm

(b)



Base value for aromatic ketone = 246 nm

Increments for:

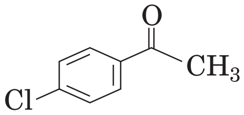
o-ring residue = 3 nm

m-OMe group = 7 nm

p-OMe group = 25 nm

∴ Calculated λ_{max} = 281 nm

(c)

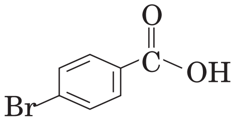


Base value for aromatic ketone = 246

Increment for *p*-Cl group = 10 nm

∴ Calculated λ_{max} = 256 nm

(d)

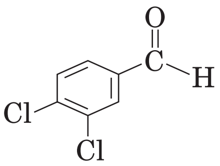


Base value for aromatic carboxylic acid = 230 nm

Increment for *p*-Br group = 15 nm

∴ Calculated λ_{max} = 245 nm

(e)



Base value for aromatic aldehyde = 250 nm

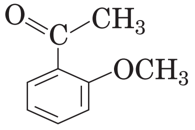
Increments for:

p-Cl group = 10 nm

m-Cl group = 0 nm

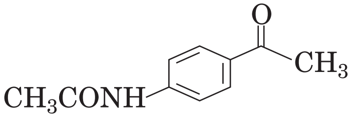
∴ Calculated λ_{max} = 260 nm

(f)



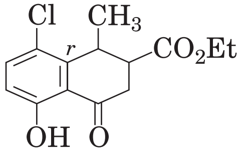
Base value for aromatic ketone = 246 nm
Increment for *o*-OMe group = 7 nm
∴ Calculated λ_{max} = 253 nm

(g)



Base value for aromatic ketone = 246 nm
Increment for *p*-NHAc group = 45 nm
∴ Calculated λ_{max} = 291 nm

(h)

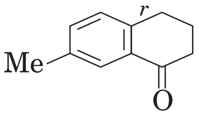


Base value for aromatic ketone = 246 nm

Increments for:

o-ring residue = 3 nm
o-OH group = 7 nm
m-Cl substituent = 0 nm
∴ Calculated λ_{max} = 256 nm

(i)



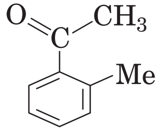
Base value for aromatic ketone = 246 nm

Increments for:

o-ring residue = 3 nm
m-alkyl substituent = 3 nm
∴ Calculated λ_{max} = 252 nm

25. An aromatic ketone ($C_9H_{10}O_2$) gives positive iodoform test but does not give any test for phenolic —OH. The observed λ_{max} value of the compound is 274 nm. Predict the structure of the ketone.

Solution Since the ketone gives positive iodoform test, therefore, it must contain a —$COCH_3$ group. The molecular formula of acetophenone ($PhCOCH_3$) is C_8H_8O. Therefore, the compound must have a ($C_9H_{10}O_2 - C_8H_7O = OCH_3$) —$OCH_3$ group and so, it does not give a test for phenolic —OH. Thus, the given compound is any one of the three isomeric (*ortho*-, *meta*- and *para*-) methoxyacetophenone. Now, the λ_{max} values of the three compounds may be calculated as follows:



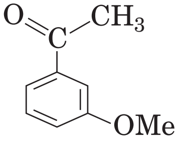
o-Methoxyacetophenone

Base value = 246 nm

Increment for

o-OMe group = 7 nm

∴ λ_{max} = 253 nm



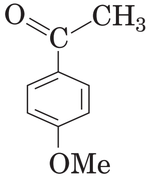
m-Methoxyacetophenone

Base value = 246 nm

Increment for

m-OMe group = 7 nm

∴ λ_{max} = 253 nm



p-Methoxyacetophenone

Base value = 246 nm

Increment for

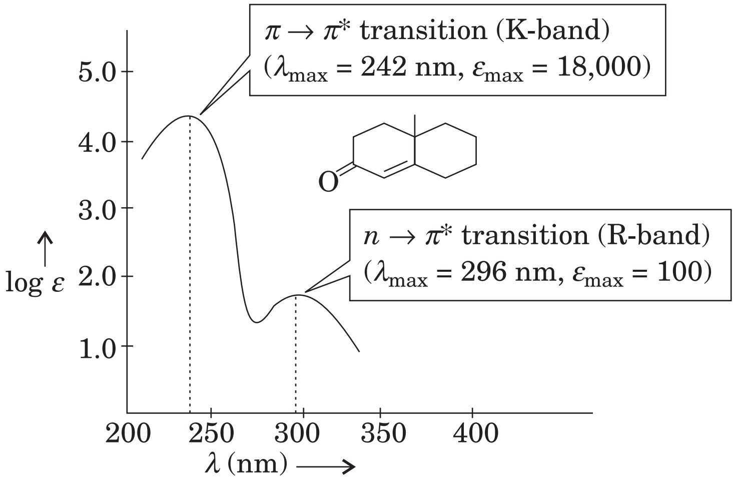
p-OMe group = 25 nm

∴ λ_{max} = 271 nm

Since the calculated λ_{max} for *p*-methoxyacetophenone (271 nm) is very close to the given value (274 nm), the compound is *p*-methoxyacetophenone.

26. What do you mean by λ_{max} and ε_{max} values in a UV spectrum? Explain your answer with a suitable diagram of an α,β-unsaturated ketone.

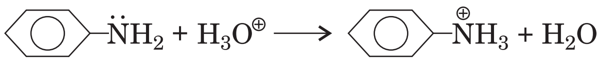
Solution The wavelength corresponding to maximum absorption (maxima of the curve) is denoted as λ_{max} and the intensity of absorbance at that wavelength is expressed as ε_{max}. A typical UV spectrum is shown below, where the compound has undergone both $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, is given as follows.



27. Predict and explain the following changes in the auxochromic red/blue shifts: (a) when $PhNH_2$ is acidified (b) when PhOH is basified and (c) when PhCOOH is basified.

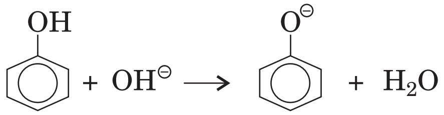
Solution

(a) In acid, $\mathrm{Ph\ddot{N}H_2}$ undergoes protonation to give $\mathrm{Ph\overset{\oplus}{N}H_3}$. The unshared electron pair on nitrogen is no longer available in $\mathrm{Ph\overset{\oplus}{N}H_3}$. As a result, the resonance interaction with the ring does not take place and absorption now occurs at a shorter wavelength (blue shift). λ_{max} of $PhNH_2$ is 230 nm, whereas that of $Ph\overset{\oplus}{N}H_3$ is 203 nm (similar to benzene).


$\ddot{N}H_2 + H_3O^{\oplus} \longrightarrow$
$\overset{\oplus}{N}H_3 + H_2O$

Aniline Anilinium ion

(b) Phenol reacts with base to form phenoxide ion.



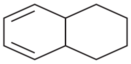
Phenol Phenoxide ion

Since, in $PhO^{\ominus}$, there is a full-fledged negative charge on oxygen, $—O^{\ominus}$ is a better electron donor than —OH. As a consequence, resonance interaction with the ring is highly increased and the absorption shifts to a longer wavelength (red shift), from 210 to 235 nm.

(c) Benzoic acid (PhCOOH) reacts with base to form its conjugate base $PhCOO^{\ominus}$. The $—COO^{\ominus}$ group, because of its full negative charge (causing effective resonance interaction within itself), becomes a poorer electron-withdrawing group. As a consequence, resonance interaction with the ring is decreased and absorption occurs at a shorter wavelength (blue shift), from 230 to 224 nm.

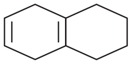
28. How would you distinguish between the two compounds in each of the following pairs by UV spectroscopic studies?

(a)



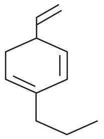
I

and



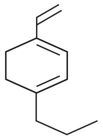
II

(b)



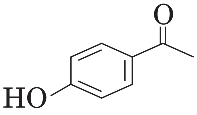
III

and



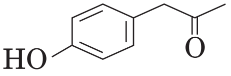
IV

(c)



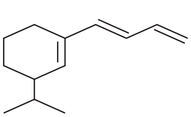
V

and



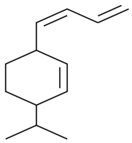
VI

(d)



VII

and



VIII

Solution

(a) In compound I, the two double bonds are conjugated and present in a ring, i.e., it is a homoannular diene. Hence, it exhibits λ_{max} at around 253 nm. But the compound II is not a conjugated diene. So, it will not show any characteristic absorption in the UV-region.

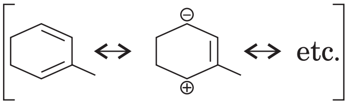
(b) The compound III is a homoannular diene with one alkyl substituent. The third double bond is not conjugated with the homoannular diene system. Therefore, the compound is expected to exhibit a λ_{max} around 253 + 5 = 258 nm. In compound IV, all the three double bonds are conjugated. It is also a homoannular diene with one alkyl substituent. Therefore, the compound is expected to exhibit a λ_{max} around 253 + 30 + 5 = 288 nm. Hence, they can be easily distinguished by UV spectral analysis.

(c) The compound V is an aromatic ketone with a *para* —OH group. So, a characteristic absorption band at about (246 + 25) = 271 nm is expected to be observed. On the other hand, in the compound VI, the acyl group is not directly attached to the benzene ring. So, this compound is expected to exhibit spectrum similar phenol (λ_{max} 210 nm). Thus, they can be easily differentiated by UV spectral analysis.

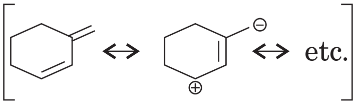
(d) The compound VII contains three double bonds which are conjugated. Also, it contains two ring residues. So, the compound is expected to exhibit λ_{max} near (217 + 30 + 10) = 257 nm. In compound VIII, on the other hand, out of three double bonds two are in conjugation (ring double bond is not conjugated with the other two). The diene system contains one alkyl substituent. Therefore, the compound is expected to exhibit λ_{max} at about (217 + 5) = 222 nm. Thus, they can be easily distinguished by UV spectral studies.

29. ε_{max} of a heteroannular diene is greater than a homoannular diene for $\pi \rightarrow \pi^*$ transition, although the order of λ_{max} is opposite. Explain.

Solution The intensity of absorption increases with increase in transition moment (dipole moment during electron transition). In the ground state, the more stable resonance structure is the important contributor to decide the ground state dipole moment. On the other hand, the excited state resembles the less stable resonance structure which may be considered as the important contributor to determine the excited state dipole moment. In a homoannular diene (with *cisoid* geometrical arrangement of conjugated diene), the charge separated resonance structure shows the separation of charge at a smaller distance compared to that of a heteroannular diene (with *transoid* geometry of diene). Thus, the transition moment of the heteroannular diene is greater than that of homoannular diene and because of this, ε_{max} of the former is greater than the latter for $\pi \rightarrow \pi^*$ transition, although the order of λ_{max} is opposite.



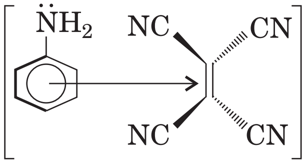
A homoannular diene



A heteroannular diene

30. Charge–transfer complexes are usually dark coloured. Explain with an example.

Solution In charge transfer complexes, the HOMO of the donor molecule interacts with the matching LUMO of the acceptor molecule to form new molecular orbitals of the adduct. This results in a drop in ΔE for electron transition. As a consequence, the λ_{max} shifts to a longer wavelength (visible region). Also, due to enhanced dipolar character in the complex, the transition moment in increased and so, the intensity of absorption is increased. For this reason, charge-transfer complexes are usually dark coloured. For example, when tetracyanoethylene (colourless) is added to a colourless solution of aniline, it becomes deep blue due to formation of a charge-transfer complex as shown below:

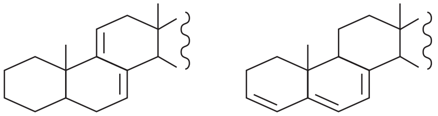


Charge–transfer complex
(deep blue)

31. Distinguish *cis*-stilbene and *trans*-stilbene by UV-spectroscopy. [CU 2010]

Solution See **article no. 4.2.13**

32. How can you distinguish the following molecules by UV-spectroscopy? [CU 2010]



Solution See the answer to the **solved problem 19**.

33. The UV spectrum of mesityl oxide shows absorption bands at 230 nm (ε 12,600) and 329 nm (ε 41) in hexane. Assign them in terms of electronic transitions. How do the absorption bands change their positions in water as solvent? [CU 2011]

Solution See the answer to the **solved problem 16** and **article no. 4.2.9**.

34. How *o*-nitroaniline can be distinguished from *p*-nitroaniline by UV-spectroscopy?

Solution See the answer to the **solved problem 10**.

35. Explain why a polar solvent usually shifts the $\pi \rightarrow \pi^*$ transition to longer wavelengths. [CU 2013]

Solution See **article no. 4.2.9**.

36. How would you distinguish 4-nitro-*N*,*N*-dimethylaniline and acidified 4-nitro-*N*,*N*-dimethylaniline by UV-spectroscopy? [CU 2014]

Solution See the answer to the **solved problem 28(a)**.

37. Define the following terms:
(i) hypochromic effect (ii) hypsochromic effect [CU 2014]

Solution See **article no. 4.2.2.**

STUDY PROBLEMS

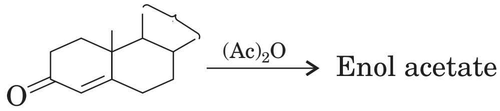
1. (a) Discuss the theory of electronic spectroscopy. What is its absorption range?
   (b) Give the various types of transitions involved in electronic spectroscopy with one example in each case.

2. Define the following terms:
(a) Chromophore (b) Auxochrome (c) Bathochromic shift
(d) Hypsochromic shift (e) Hyperchromic effect (f) Hypochromic effect
(g) Molar absorptivity

3. Explain the following observations:
(a) Polar solvents usually shift the $\pi \rightarrow \pi^*$ transition to longer wavelength and $n \rightarrow \pi^*$ transition to shorter wavelength.
(b) λ_{max} of the benzenoid bond shift to longer wavelength as the number of linearly fused benzene ring increases.
(c) *p*-Nitroaniline absorbs at a longer wavelength compared to its *ortho*- or *meta*-isomers.
(d) The intensity of $\pi \rightarrow \pi^*$ transition is 10 to 100 times stronger than $n \rightarrow \pi^*$ transition.
(e) The position of absorption of acetone ($n \rightarrow \pi^*$ transition) shifts in different solvents: 279 nm (hexane); 272 nm (ethanol) and 264.5 nm (water).

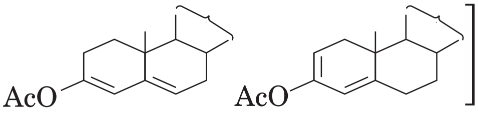
4. Relate resonance effect, hyperconjugative effect, H-bonding effect, and steric effect to the position of absorption.

5. Cholest-4-en-3-one gives an enol acetate which has λ_{max} at 238 nm. Predict the structure of the enol ester.



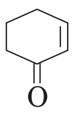
Cholest-4-en-3-one

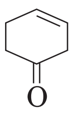
[**Hint:** The two possible enol acetates that can be formed are as follows:

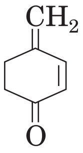


]

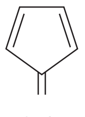
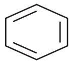
6. Which of the following carbonyl compounds would you expect to absorb light of longest and shortest wavelengths? Give your reasoning.

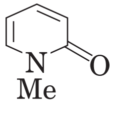
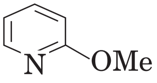

A


B


C

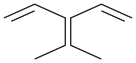
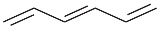
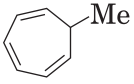
7. Compare the expected λ_{max} values of the following pairs and explain:

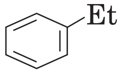
(a)  and 

(b)  and 

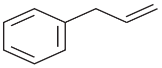
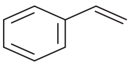
(c) $PhCH_2OCH_3$ and $PhOCH_2CH_3$

(d) p-$O_2NC_6H_4CH_2NHCH_3$ and p-$O_2NC_6H_4NMe_2$

(e)  and  (f) 

and 

(g) $CH_2{=}C{=}CH_2$ and $CH_2{=}CH{-}CH{=}CH_2$

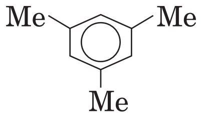
(h)  and 

8. Account for the following observations:

(a) A bathochromic shift is observed when a solution of aniline ($PhNH_2$) in dilute HCl is neutralised by dilute NaOH.

(b) A hypsochromic shift is observed when a solution of 2-hydroxypyridine is made alkaline.

(c) The value of λ_{max} of the compound I is almost same as that of the compound II. However, the absorbance of the former is nearly twice of the latter.



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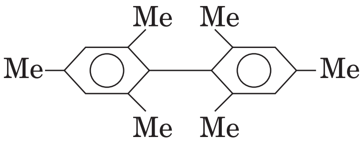


II

(d) λ_{max} of the aqueous solution of p-aminophenol shifts to shorter wavelength when the solution is acidified with dilute hydrochloric acid.

(e) The colour of the aqueous suspension of p-nitrophenol changes from light yellow to intense yelled when NaOH solution is added to it.

(f) λ_{max} of 2-methylbiphenyl (237 nm, ε_{max} = 10,250) is shorter than biphenyl (250 nm, ε_{max} = 19,000).

9. "A conjugated diene absorbs at a higher wavelength with higher value of extinction coefficient as compared to a diene in which the double bonds are isolated." Comment on this statement giving the chemistry involved.

10. The *cis*-isomer of cinnamic acid absorbs at 268 nm (ε_{max} = 10,700), while its *trans*-isomer absorbs at 272 nm (ε_{max} = 15,900). Explain the hypsochromic shift in the UV spectrum of the *cis*-isomer with respect to the *trans*-isomer.

11. Explain the following observations:

(a) $\sigma \rightarrow \sigma^*$ transition cannot be accessible by ordinary spectrophotometer.

(b) $n \rightarrow \pi^*$ transition is a forbidden transition.

(c) Deepening of colours occurs with increasing conjugation.

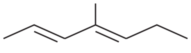
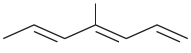
(d) Ethylene shows two λ_{max} values.

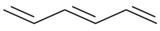
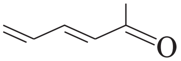
(e) Spectrophotograph of an electronic excitation is a curve instead of a series of discrete lines.

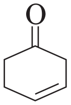
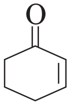
(f) The λ_{max} value increases on going from left to right in the following series:

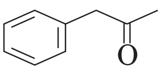
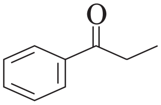
PhOH (210 nm), PhOMe (217 nm), $PhO^{\ominus}$ (235 nm)

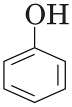
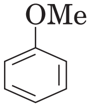
12. How could you distinguish between the compounds in each of the following pairs using UV spectroscopy?

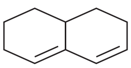
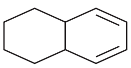
(a)  and 

(b)  and 

(c)  and 

(d)  and 

(e)  and 

(f)  and 

13. Indicate which of the following compounds would be suitable as solvents for recording normal UV spectra of substrates and briefly explain your choices: ethanol, perfluoropropane, 1-chlorobutane, diethyl ether, ethyl iodide, methylene bromide, methyl butyl sulfide, benzene, cyclohexane and acetonitrile.

14. Account for the following observations:

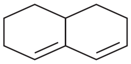
(a) Deprotonation of phenol results in a red shift.

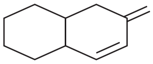
(b) The absorption band at 227.3 nm for $\mathrm{Me_3\ddot{N}}$ disappears in acid solution.

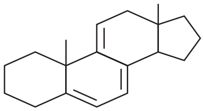
(c) 1,5-Hexadiene does not absorb light above 200 nm.

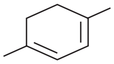
(d) MeI (λ_{max} 258 nm) absorbs at a much longer wavelength compared to MeBr (λ_{max} 204 nm).

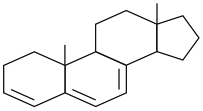
15. Match the following λ_{max} values with the corresponding compounds: (i) 232 nm, (ii) 237 nm, (iii) 273 nm, (iv) 283 nm, (v) 313 nm, (vi) 353 nm.

(a) 

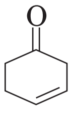
(b) 

(c) 

(d) 

(e) 

16. For each of the following compounds, write down the structure of an isomer that is likely to have a substantially different UV spectrum:



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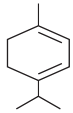

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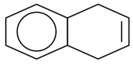

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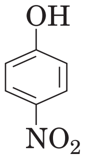
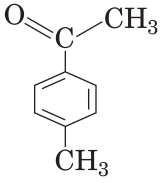
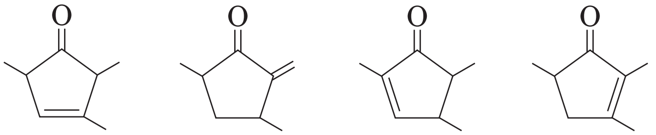


IV

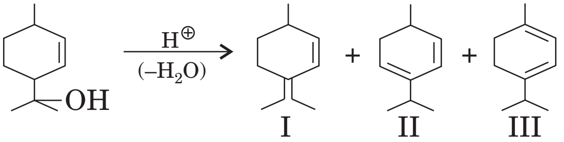


V

17. A ketone has λ_{max} (in EtOH) at 224 nm. It was known to have one of the following isomeric structures. Identify it.



18. How would you distinguish the three dienes obtained in the following reaction (acid-catalyzed dehydration of a 3° alcohol) by calculating λ max values?



4.3 INFRARED SPECTROSCOPY

Introduction

The infrared (IR) spectroscopy has been most widely used to get information about the structure of an unknown organic compound. Organic chemists actually use infrared spectroscopy to identify the functional groups in a compound. There are a number of bands in a typical IR spectrum and only a few of them are to be studied for determining the presence or absence of many common functional groups.

4.3.1 Basic Principle of IR Spectroscopy

Infrared radiation (λ = 2.5 – 15.4 μm) is the energy source in IR spectroscopy. The infrared (from the Latin, infra, meaning 'below' red) region of the spectrum corresponds to frequencies from just below the visible frequencies to just above the highest microwave and radar frequencies. Infrared photons do not have enough energy to cause electronic transition. However, they can cause groups of atoms to vibrate with respect to the bonds that connect them. Like electronic transitions, these vibrational transitions correspond to distinct energies, and molecules actually absorb infrared radiation only at certain wavelengths and frequencies. Frequencies in IR spectroscopy are reported using a unit called the wave number $(\bar{\nu})$. Wave number is simply the inverse of the wavelength $\left(\bar{\nu} = \frac{1}{\lambda}\right)$ and reported in reciprocal centimetres (cm^{-1}). Wave number $(\bar{\nu})$ is proportional to frequency (ν) which in turn is proportional to energy. Frequency (and therefore energy) increases with increase in wave number. Using the wave number scale, IR absorptions occur from 4000 cm^{-1} to 650 cm^{-1}.

To apply the equation $\bar{\nu} = 1/\lambda$ in reciprocal centimetres units, we must include the conversion factor 10^4 μm · cm^{-1}. In the convenient units, then, this equation becomes

$$\bar{\nu}(\text{in cm}^{-1}) = \frac{10^4\ \mu\text{m}\cdot\text{cm}^{-1}}{\lambda\ (\text{in }\mu\text{m})}$$

or

$$\lambda(\text{in }\mu\text{m}) = \frac{10^4\ \mu\text{m}\cdot\text{cm}^{-1}}{\bar{\nu}(\text{in cm}^{-1})}$$

[The relationships among wave number $(\overline{\nu})$, energy (E) and frequency (ν) can be shown as follows:

$$\nu = \frac{c}{\lambda} = c\overline{\nu}\ ;\ E = h\nu = \frac{hc}{\lambda} = hc\overline{\nu}\ ]$$

4.3.1.1 Molecular Vibrations

Covalent bonds are not static. Various atoms in a molecule may be regarded as balls and the covalent bonds, connecting these atoms, as weightless springs holding such balls together. Because of the springlike nature, atoms in a molecule do not stay at fixed positions with respect to each other, but actually vibrate back and forth about an average value of the interatomic distance. Therefore, the covalent bonds obey Hook's law for harmonic oscillators. It is to be noted that various vibrations, being quantized, have definite frequency of their own and when the radiation of the same frequency is passed through the molecule, there is an absorption of energy resulting in the increase of the amplitude of that particular vibration. Generally, **such absorption of an infrared light quantum can occur only if the dipole moment of the molecule is different in the two vibrational levels.** The variation of dipole moment with change in interatomic distance during vibration corresponds to an oscillating electric field that can interact with the oscillating electric field associated with the electromagnetic radiation and when the phase of one field matches with the phase of the other, absorption occurs; the absorption is maximum when the frequencies of these two oscillating electric fields become identical. So, the condition for maximum absorption of radiation is:

$$\text{Frequency of radiation, } \nu = \text{frequency of vibration, } \omega$$

This frequency of radiation is known as the **fundamental tone**. The radiations having frequencies 2ω, 3ω, etc. are known as overtones. The degree of absorption of such radiations is actually very low.

4.3.1.2 IR-Active and IR-Inactive Vibrations

In general, molecular vibrations which lead to a change in the dipole moment of the molecule will give rise to absorption band in the IR spectrum. Vibrations of bonds with dipole moments generally result in IR absorptions and are said to be **IR active**. If a bond is symmetrical and has zero dipole moment, the vibration produces no change in the dipole moment and so, there is no absorption of energy. This vibration is said to be **IR inactive**, and it produces no absorption in the IR spectrum. Therefore, the key to an IR-active vibration is that *the vibration must change the dipole moment of the molecule*. The triple bond of acetylene (H—C≡C—H) has zero dipole moment, and the dipole moment remains zero if the bond is stretched or compressed. This vibration is, therefore, said to be IR inactive. Similarly, the symmetric stretching vibration of CO_2 is IR inactive because it produces no change in the dipole moment of the molecule.

4.3.1.3 Molecular Vibrations from Quantum Theory

The energy of different quantised vibrational levels may be expressed by the following equation by applying quantum mechanics:

$$E_{\text{vib}} = \left(V + \frac{1}{2}\right)h\omega$$

where V is the number of vibrational levels and can have values 0, 1, 2, 3, etc. (the energy level where $V = 0$ is known as zero point energy level), h = Planck's constant and ω (omega) = vibrational frequency. Transitions from ground state ($V = 0$) to the first excited state ($V = 1$) absorbs light strongly and give rise to intense bands called the *fundamental bands*. The energy difference ΔE_{vib} between the lowest possible energy level and the next higher energy level is:

$$\begin{aligned}\Delta E_{\text{vib}} &= E_{\text{vib}(V=1)} - E_{\text{vib}(V=0)} \\ &= \left(1 + \frac{1}{2}\right)h\omega - \left(0 + \frac{1}{2}\right)h\omega \\ &= \frac{3}{2}h\omega - \frac{1}{2}h\omega = h\omega\end{aligned}$$

Absorptions corresponding to higher energy excitations (e.g., $V_0 \rightarrow V_2$) are called overtones. Assuming that all the vibrational bands are equally spaced (in fact, these are not), the energy of the first overtone is given by:

$$\begin{aligned}\Delta E_{\text{vib}} &= E_{\text{vib }(V=2)} - E_{\text{vib }(V=0)} \\ &= \left(2 + \frac{1}{2}\right)h\omega - \left(0 + \frac{1}{2}\right)h\omega \\ &= 2\,h\omega\end{aligned}$$

The amount of *zero point energy* $E_{\text{vib }(V=0)} = \frac{1}{2}h\omega$. This indicates that even at the lowest vibrational energy level the atoms are not at rest. Instead they oscillate along the bond axis with frequency, ω, with a particular amplitude. The bond length is regarded as to average distance during such oscillation. Figure 4.9 shows the diagram representing various energy levels corresponding to interatomic oscillation along a bond, say A—B, with variable amplitudes. The different probable positions of the atom A, at different energy levels are represented by dots on the energy axis. Pair of dots on each line represents the extreme probable positions of the atom B during contraction and extension of the bond A—B. It is to be noted that the positions of A and B as shown in the diagram are not their exact positions, but their most probable positions.

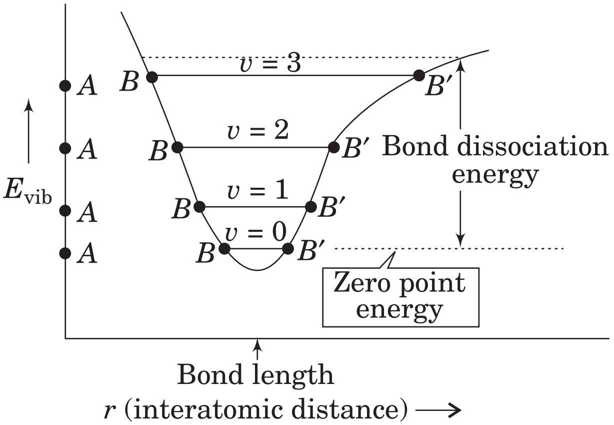


Figure 4.9 Energy diagram of interatomic oscillations

If the amplitude of vibration is very high, the bond dissociates into two atoms. The difference of energy between the highest vibrational level and the zero point energy level is known as the *bond dissociation energy* of that bond. In the case of bonds containing different isotopes such as C—H and C—D, the highest vibrational energy level is constant; the bond containing the isotope has higher bond dissociation energy because its zero point energy is low.

For a linear molecule of n atoms, the vibrational degrees of freedom can be calculated as follows:

Total degrees of freedom = $3n$

Translational degrees of freedom = 3

Rotational degrees of freedom = 2

∴ Vibrational degrees of freedom = $(3n - 3 - 2) = (3n - 5)$

Hence, theoretically there will be $(3n - 5)$ possible fundamental bands for the linear molecules. For example, in the linear molecule CO_2, the number of vibrational degrees of freedom is $(3 \times 3 - 5) = 4$. Hence, for CO_2, the theoretical number of fundamental bonds should be equal to four.

For a non-linear molecule of n atoms, there are three degrees of rotation. Therefore, the vibrational degrees of freedom = $(3n - 3 - 3) = (3n - 6)$. For example, in the non-linear molecule C_6H_6, the number of vibrational degrees of freedom is $(3 \times 12 - 6) = 30$. So, theoretically there should be 30 fundamental bands in the IR spectrum of benzene.

It has been observed that the theoretical number of fundamental vibrations are seldom obtained. It is because of the following reasons:

(i) Fundamental vibrations that fall outside the region under investigation, i.e., 2.5–15.4 μm.

(ii) Fundamental vibrations that are too weak to be observed as bands.

(iii) Fundamental vibrations that are so close that they overlap, i.e., degenerate vibrations.

(iv) Certain vibrational bands do not appear for want of the required change in the dipole moment in a molecule.

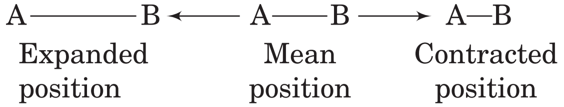
There may appear some less intense (10–100 times less intense as compared to the fundamental bonds) additional bands called combination bands, difference bands and overtones. Thus, due to these, a large number of bands will be observed as compared to the theoretical number.

4.3.1.4 Types of Vibration

There are two types of molecular vibrations which are known as stretching and bending vibrations. Stretching vibrations are rhythmic back and forth movement of atoms along the covalent bond axis and in this process the distance between the atoms increases and decreases. Bending vibrations occur in the molecule having more than two atoms which are not directly connected by a covalent bond and may involve a change in bond angles between bonds with a common atom. Stretching vibrations require more energy than bending vibrations and hence, occur at lower wavelength or higher wave number than bending vibrations.

Various types of vibrations may be shown pictorially as follows:

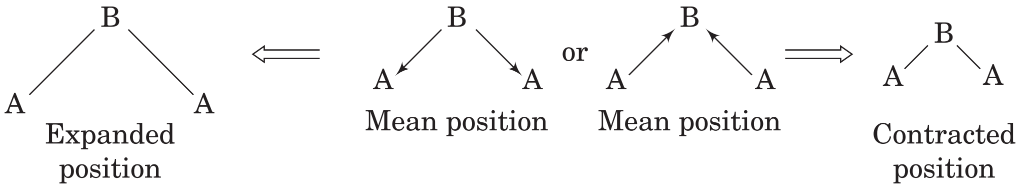
(i) Two atoms joined by a covalent bond can undergo a stretching vibration where the atoms move back and forth as if joined by a spring.



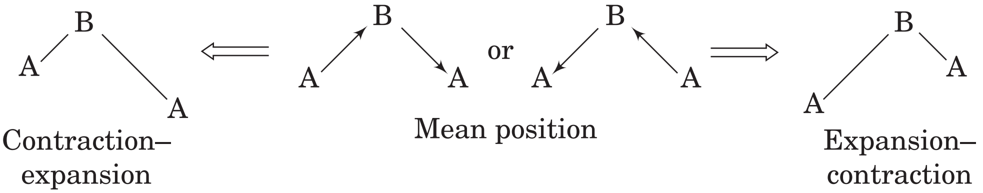
(ii) Molecules containing more than two atoms undergo stretching as well as bending vibrations.

Stretching vibrations:

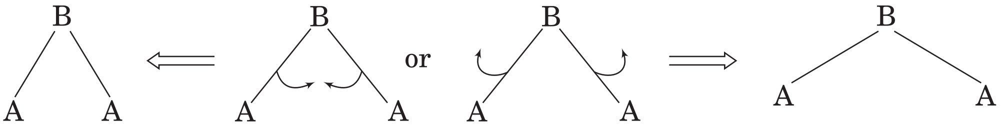
(a) *Symmetric stretching:*



(b) *Asymmetric stretching*



Bending vibrations (deformations)



Bond angle decrease

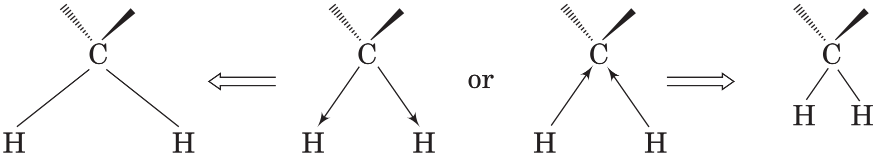
Mean position

Bond angle increase

The stretching and bending vibrations for two atoms joined by a covalent bond around tetrahedral carbon (a methylene group, $>CH_2$) are as follows:

Stretching vibrations

(a) *Symmetric stretching*

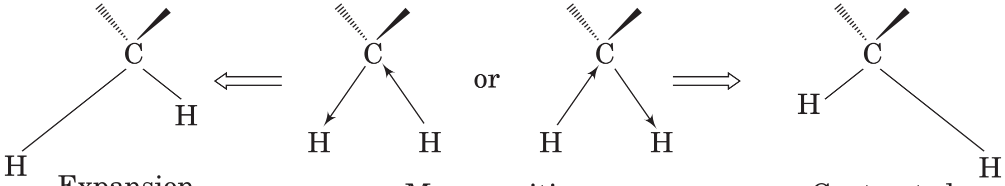


Expanded position

Mean position

Contracted position

(b) *Asymmetric stretching*



Expansion–contraction

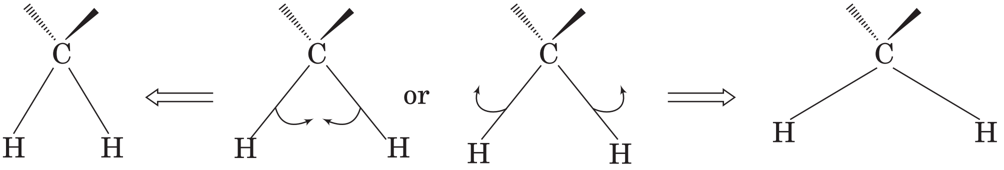
Mean position

Contracted–expansion

Bending vibrations

(a) *In-plane bending vibrations*

(i) **Scissoring**

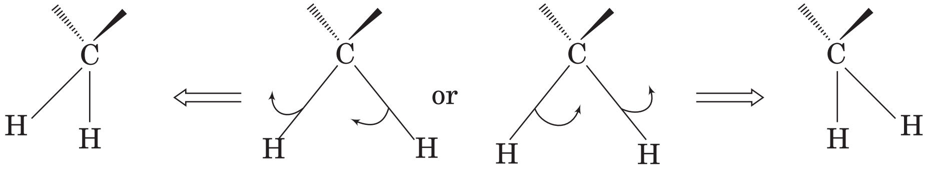


Bond angle decrease

Mean position

Bond angle increase

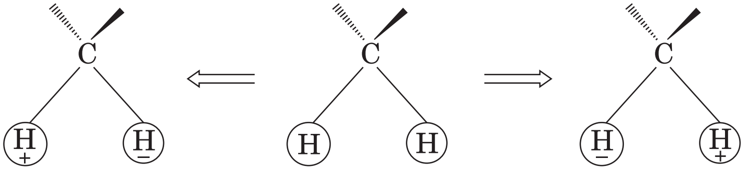
(ii) **Rocking**



Mean position

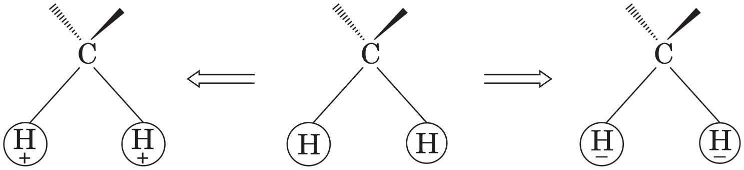
(b) *Out-of-plane bending vibrations*

(i) **Twisting**



Mean position

(ii) **Wagging**



Mean position

[+ and – signs represent vibrations perpendicular to the plane of the paper.]

4.3.2 IR Spectrum

In an infrared spectrophotometer, IR radiation of successively increasing wavelength is passed through the sample of the compound and the percent transmittance is measured. An IR spectrum generally shows the change of transmittance with frequency expressed as wave numbers (cm^{-1}). Each dip in a spectrum is called a band or peak and that represents absorption of IR radiation by the sample at that frequency. A 100% transmittance means no absorption and if all the radiation is absorbed, the transmittance is 0%.

An IR spectrum may roughly be divided into two regions. Absorptions from 4000 to 1430 cm^{-1} involve changes in the vibrational states of various bonds and are generally characteristic of the type of bonds (such as O—H, N—H, C=O, etc.) present in the molecule. There are relatively few peaks in this part and their position is only slightly changed by the rest of the molecule. This region of IR spectrum is called the *group frequency region*, and is very helpful for the identification of functional groups. Absorption bands between 1430 to 910 cm^{-1} are more numerous and are associated with a number of vibrational and rotational energy changes in the molecule and are less valuable for the identification of the functional groups. However, this region (called the *finger print region* because the pattern of absorptions in this region are unique to any particular compound, just as a person's finger prints are unique) is quite characteristic of the molecule as such and is extremely useful in determining the identity between two samples. Substances that give the same (superimpossable) infra red spectra are identical. This proof of identity is far more reliable than the comparison of any other physical property (e.g., mixed m.p. determination). The IR spectrum of 1-propanol, $CH_3CH_2CH_2OH$, is shown in Figure 4.10.

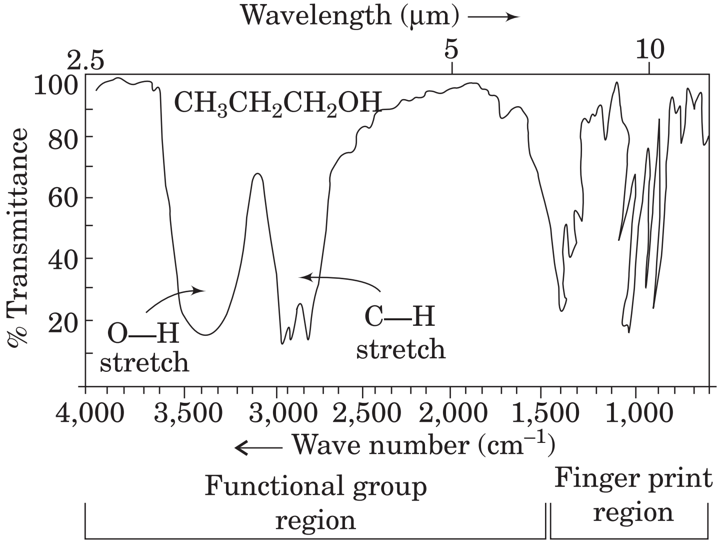


Figure 4.10 IR spectrum of 1-propanol ($CH_3CH_2CH_2OH$)

4.3.3 Factors that Determine IR Absorption Position

The factors that govern the position of IR absorption are as follows:

1. Strength of the bond
2. Masses of the atoms involved in the bond
3. The type of vibration

The first two of these effects may nicely be explained by Hooke's law, which originates from the treatment of the vibrating spring by classical physics. Let two atoms with masses M and m, respectively, are connected by a bond which can be treated as a spring. The stiffness of the spring (bond) is described by a force constant, K: the larger the force constant, the tighter the spring, or stronger the bond.

The natural frequency of vibration of a bond is given by the equation

$$\bar{v} = \frac{1}{2\pi c}\sqrt{\frac{K}{\mu}}$$

which is derived from Hooke's law for vibrating spring. The *reduced mass* μ of the system is given by

$$\mu = \frac{m_1 m_2}{m_1 + m_2}$$

From the above equation, it becomes clear that atoms connected by a stronger bond (large force constant) vibrate at higher frequency. In general, triple bonds are stronger than double bonds which in turn are stronger than single bonds between the same two atoms, and therefore, frequency of vibration gradually increases on going from single to triple bond.

	C—C	C=C	C≡C
$\bar{v}$:	1,200 cm^{-1}	1,650 cm^{-1}	2,150 cm^{-1}

$\bar{v}$ increases with increase in force constant (K)

The second thing which should be noticeable is that bonds between atoms of higher masses (larger reduced mass, μ) vibrate at lower frequencies than bonds between lighter atoms. The C—H stretching occurs at about 3,000 cm^{-1}. As the atom bonded to carbon increases in mass, the reduced mass (μ) increases, and the frequency of vibration decreases (i.e., wave numbers get smaller).

	C—H	C—C	C—O	C—Cl	C—Br	C—I
$\bar{v}$:	3000 cm^{-1}	1200 cm^{-1}	1100 cm^{-1}	750 cm^{-1}	600 cm^{-1}	500 cm^{-1}

$\bar{v}$ decreases with increase in reduced mass (μ)

Suppose the two atoms connected by a bond differ significantly in mass (for example, a C and an H atom in a C—H bond) and also suppose in the above equation that $m_1 >> m_2$. In such a case, the smaller mass m_2 can be ignored in the numerator of this equation and the larger mass m_1 then cancels and vanishes from the equation, leaving only the smaller mass m_2 in the denominator. The equation then becomes

$$\bar{v} = \frac{1}{2\pi c} = \sqrt{\frac{K}{m_2}}$$

This equation says that the vibration frequency of a bond between a heavy and a lighter atom depends primarily on the mass of the lighter atom. For this reason, C—H, O—H, and N—H bonds all absorb in the same general region of the IR spectrum. In fact, the difference that actually exist between the vibrational frequencies of these bands are not due to mass effects, but due to bond-strength effects.

The third factor that affects the absorption frequency is the type of vibration. This has already been discussed in **article no. 4.3.1.4**.

Calculation of stretching frequency

The stretching frequency of a C—H bond in wave number (cm^{-1}) may be calculated as follows:

$$\bar{v} = \frac{1}{2\pi c} = \sqrt{\frac{K(m_1 + m_2)}{m_1 m_2}}$$

mass of a carbon atom (m_1) = 20×10^{-24}

mass of a hydrogen atom (m_2) = 1.6×10^{-24} g

The force constant (K) of a C—H bond = 5.0×10^5 g sec^{-2}

The velocity of light (c) = 3.0×10^8 m sec^{-1}

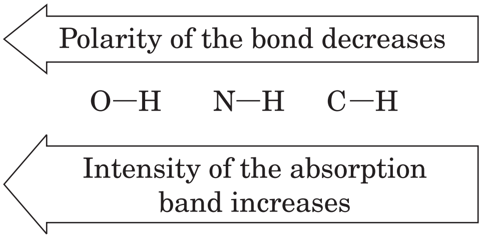
$$\bar{v} = \frac{1}{2 \times 22/7 \times 3 \times 10^8 \text{ m sec}^{-1}} \left[\frac{5.0 \times 10^5 \text{g sec}^{-2} (20 \times 10^{-24} \text{g} + 1.6 \times 10^{-24} \text{g}}{20 \times 10^{-24} \text{g} \times 1.6 \times 10^{-24} \text{g}} \right]^{\frac{1}{2}}$$

$$= 3100 \text{ cm}^{-1}$$

Actual range for C—H stretching is 2850 – 3300 cm^{-1}.

4.3.4 Factors that Determine IR Absorption Intensity

When a bond stretches, the distance between the atoms increases and as a consequence, its dipole moment increases. The intensity of the absorption band depends on the size of this change in dipole moment. *The greater the change in dipole moment*, *the more intense the absorption*. Although the absorption bands for the stretching vibrations of C═O and C═C bonds appear at similar frequencies, they can be easily distinguished. The band for C═O is much more intense because it is associated with a much greater change in dipole moment since the bond is more polar. Since the O—H bond is more polar, its stretching vibration is associated with a greater change in dipole moment than that of an N—H bond. Consequently, an O—H bond shows more intense absorption than an N—H bond. Similarly, an N—H bond shows more intense absorption than a C—H bond.



Polarity of the bond decreases

O—H N—H C—H

Intensity of the absorption band increases

The intensity of an absorption band also depends on the number of bonds responsible for the absorption. The absorption band for C—H stretching for a compound such as octyl iodide (containing 17 C—H bonds) is, in fact, more intense than for methyl iodide (containing only 3 C—H bonds).

The intensity of the absorption bands may also be affected by the concentration of the sample used to obtain an IR spectrum. Concentrated samples have greater number of absorbing molecules and therefore, they result information of more intense absorption bands.

4.3.5 Functional Group Infrared Absorptions and Environmental Effects on Them

The force constant, i.e., the strength of a particular type of bond is not actually constant. Electronic effects such as resonance, inductive, etc., H-bonding effect and steric effect of the atoms or groups within the molecule have profound influence on the strength of a bond, i.e., on its force constant. Thus, in general, a particular group will not have a fixed maximum absorption but will have a region of absorption; the actual maximum absorption in this region depends on the rest of the molecule. Let us discuss some of the characteristic bands of a few functional groups and the decrease and increase in stretching frequencies due to structural changes.

1. Hydrocarbons

A. Alkanes A strong absorption band 2850–3000 cm^{-1} (centred about 2,925 cm^{-1}) represents the C—H stretching absorption. Three other bands due to C—H bending absorption appear at approximately 1,465 cm^{-1} (CH_2 group), 1,375 cm^{-1} (CH_3) group and 720 cm^{-1} (due to bending motion associated with four or more CH_2 groups in an open chain; called a *long-chain band*). C—C stretching absorption is not interpretatively useful. The IR spectrum of decane, for example, may be shown as follows (Figure 4.11):

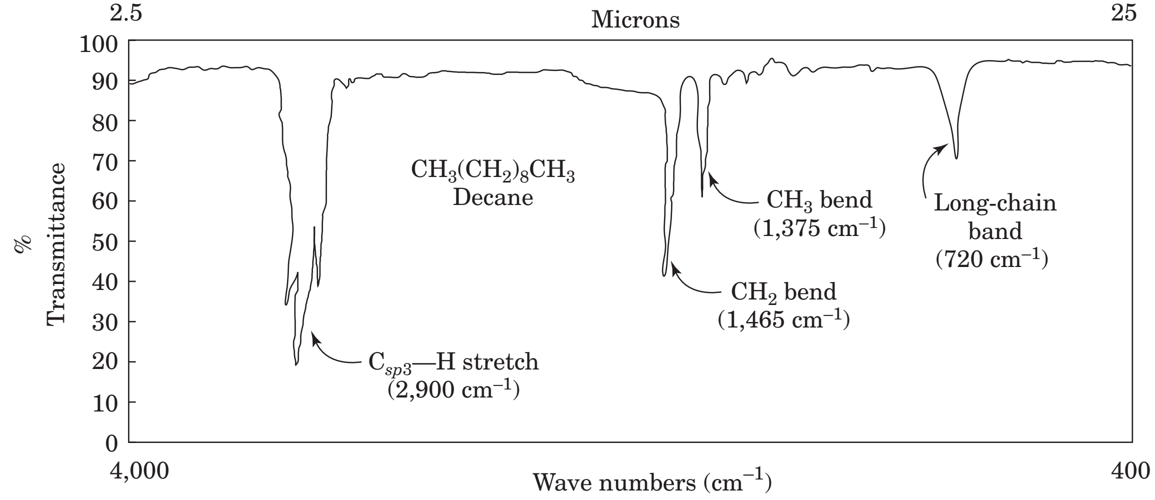
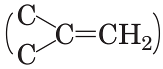
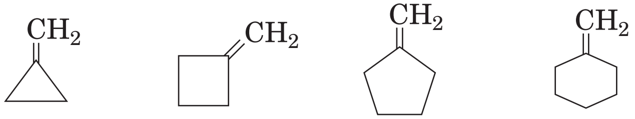


Figure 4.11 Infrared spectrum of decane (neat liquid, KBr plates

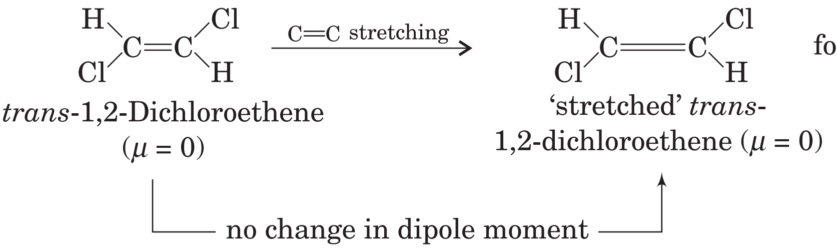
B. Alkenes In alkenes, sp^2C—H stretching absorption band appears in the region 3,000 – 3,100 cm^{-1}. An out of plane bending absorption occurs in the range 650–1000 cm^{-1}. For *trans*-alkene the C—H bending absorption occurs at 970 cm^{-1} and for *cis*-alkene at 700 cm^{-1}. This helps in distinguishing *cis*- and *trans*-alkenes. The C=C stretching vibration band appears in the region 1,600–1,680 cm^{-1}; conjugation moves C=C stretching band to lower frequencies and increases the intensity. In general, the higher the substitution on the double-bonded carbons, the higher is the frequency of absorption and lower is the intensity. The vibrational stretching frequencies of exocyclic double bonds  $\left(\overset{C}{\underset{C}{>}}C{=}CH_2\right)$ depends on the size of the ring. This is shown as follows:



$\bar{\nu}_{C=C_{str}}$: 1,780 cm^{-1} 1,678 cm^{-1} 1,657 cm^{-1} 1,651 cm^{-1}

External (exocyclic) double bonds gives an increase in absorption frequency with decreasing ring size. As the ring becomes smaller, the *p*-character of the ring forming inner orbitals of the sp^2-hybridized double-bonded ring carbon atom increases (recall the trend: $sp = 180°C$, $sp^2 = 120°$, $sp^3 = 109.5°$, $sp^{>3} = < 109.5°$) for improving the overlap with other ring forming orbitals. As a result, the *p*-character of the orbital used to form the σ-bond of the double bond decreases and consequently, the *s*-character of that orbital increases. Because of this, the stiffness of the C=C bond increases and so, the absorption frequency increases.

Symmetrically substituted *trans*-alkenes, for example, 1,2-dichloroethene, fumaric acid, etc. do not show any band for C=C stretching even though the substituted groups are highly polar. This is because each of these molecules has a dipole moment of zero, and stretching the C=C bond does not impart a dipole moment to the molecule.


H
Cl
Cl
H
C=C stretching
H
Cl
Cl
H
trans-1,2-Dichloroethene
(μ = 0)
'stretched' *trans*-
1,2-dichloroethene (μ = 0)
no change in dipole moment

(no IR absorption
for the C=C stretching
vibration)

C. Alkynes For the ≡C—H stretching vibration a strong and prominent band appears at 3300 cm^{-1}. For C≡C stretching a weak band appears at 2150 cm^{-1}.

The strength of the C—H bond decreases, with decrease in the *s*-character of the hybridization state of carbon, i.e., $C_{sp}—H > C_{sp^2}—H > C_{sp^3}—H$ and because of this, the absorption frequency decreases in the order:

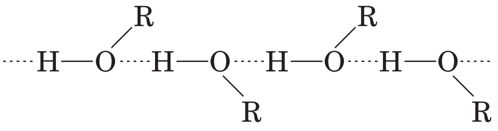
$$C_{sp}—H\ (3{,}300\ \text{cm}^{-1}) \rangle\ C_{sp^2}—H\ (3{,}000–3{,}100\ \text{cm}^{-1}) \rangle\ C_{sp^3}—H\ (2{,}800–3{,}000\ \text{cm}^{-1})$$

2. Aromatic rings

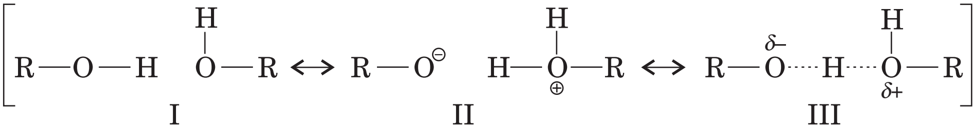
Aromatic C—H stretching band appears at 3,000–3,100 cm^{-1}. Since the C—H stretching bands for alkenes appear in the same range, it may be difficult to use the C—H stretching bands to differentiate between alkenes and aromatic compounds. However, the C=C stretching bands for aromatic rings usually appear between 1,450 and 1,600 cm^{-1} outside the usual range where the C=C appears for alkenes (1650 cm^{-1}). Also an aromatic compound must give out-of-plane C=C—H bending bands that appear in the range 690—900 cm^{-1}. This along with a weak set of bands between 1,650–2,000 cm^{-1} (overtones) help to assign substitution on the ring.

3. Alcohols and phenols

The characteristic bands observed in the spectrum of alcohols and phenols result from O—H stretching and C—O stretching. The unbonded or 'free' hydroxyl group of alcohols and phenols absorb strongly at about 3,650 cm^{-1} and this sharp bond is observed only in the vapour phase or in very dilute solution in nonpolar solvents. As the concentration of the solution increases, intermolecular H-bonding increases and the strength of the O—H bond decreases. As a result, additional band starts appearing at (lower frequencies) about 3,350 cm^{-1}, at the expense of the 'free' hydroxyl band.



Intermolecular H-bonding



Lengthening of O—H bond in hydrogen bonding

For example, the IR spectrum of ethanol in vapour state (in which there is essentially no H-bond) displays a sharp bond at 3,640 cm^{-1} which is ascribed to a free hydroxyl group. However, when the spectrum is run in solution (hydrogen bonded molecules), this sharp band is almost replaced by a broad band at 3,350 cm^{-1}. On further increasing the concentration of the solution, the band at 3,640 cm^{-1} completely disappears. The band at 3,350 cm^{-1} is the characteristics of H-bonded hydroxyl groups and since the position and intensity of this band changes with concentration it is a case of intermolecular H-bonding. The infrared spectrum of ethanol in vapour state and in concentrated solution are shown in the figures below (Figures 4.12 and 4.13).

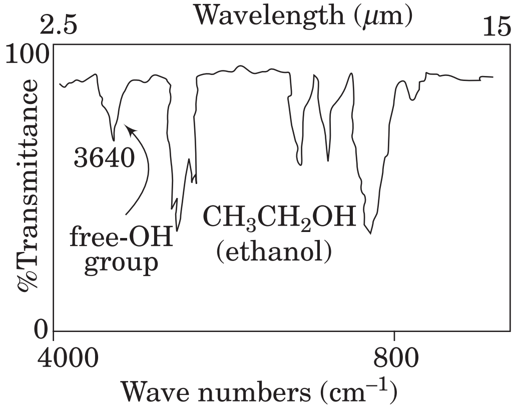


Figure 4.12 IR spectrum of ethanol (in vapour state)

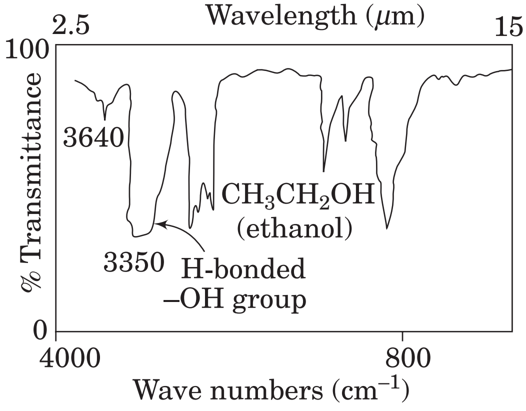
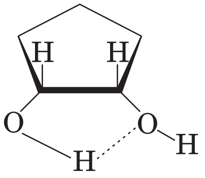


Figure 4.13 IR spectrum of ethanol (concentrated solution)

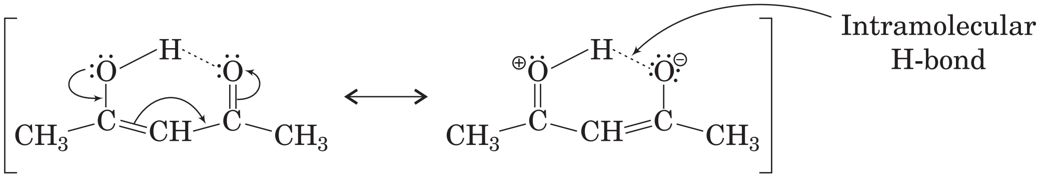
Here, it is important to note that compounds with intramolecular H-bonded groups do not lose their internal H-bonding on dilution with inert solvents like CCl_4, CS_2, etc. Therefore, a compound with internal H-bonding shows the same O—H stretching in the concentrated solution as in very dilute solution. For example, the position and intensity of the absorption band of O—H in *cis*-cyclopentane-1,2-diol (which appears at 3,450 cm^{-1}) does not change with concentration and this is because the two *cis*-OH groups are involved in intramolecular H-bonding.



cis-Cyclopentane-1,2-diol

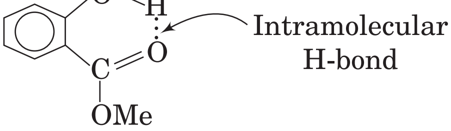
(Due to steric and dipolar repulsions of the two —OH groups, the intramolecular H-bonding is weak and causes a small shifts of O—H stretching from that of the free O—H.)

In the enols of *β*-diketones or *β*-ketoesters, the intramolecular H-bonding is exceptionally strong due to resonance and because of this, absorptions due to O—H stretching occurs at 2,500–3,100 cm^{-1}. Since these bonds are not easily broken on dilution by an inert solvent, free O—H stretching may not be seen at low concentrations. For example:



Acetyl acetone
(enol form)

Intramolecular H-bonding that occurs in *ortho*-carbonyl-substituted phenols, usually shifts the broad O—H bond to a lower frequency. For example, the O—H band in the neat spectrum of methyl salicylate is centered at about 3,200 cm^{-1}, while O—H bands from normal phenols are centered at about 3350 cm^{-1}



Methyl salicylate

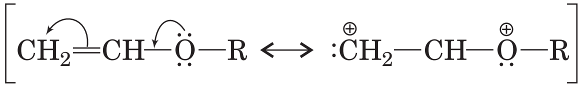
The strong C—O stretching vibrations are observed in the range from 1,000 to 1,260 cm^{-1}. The C—O stretchings of phenols appear at relatively higher frequencies as because this bond possesses some double bond character due to resonance. For example in phenol $\bar{\nu}_{C—O\ str.}$ is 1,223 cm^{-1}. Since the C—O absorptions are coupled with the adjacent C—C stretching vibrations, the position of the band may be used to assign a primary, secondary, or tertiary structure to an alcohol or to determine whether a phenolic compound is present. Table 4.6 gives the expected stretching frequencies for the C—O band in alcohols and phenols. The O—H stretching values are also given for comparison.

Table 4.6 C—O and O—H stretching vibrations in alcohols and phenols

Compound	C—O *str* (cm^{-1})	O—H *str* (cm^{-1})
1° Alcohol (saturated)	1,050	3,640
2° Alcohol (saturated)	1,100	3,630
3° Alcohol (saturated)	1,150	3,620
Phenols	1,220	3,610

4. Ethers

In alkyl ethers (R—O—R) a very strong band appears usually at about 1120 cm^{-1} for asymmetric C—O—C stretching. the symmetric stretching is IR inactive. Aryl alkyl ethers (Ar—O—R) give rise to two strong bands: an asymmetric C—O—C stretching near 1250 cm^{-1} and a symmetric stretching near 1040 cm^{-1}. Vinyl alkyl ethers ($CH_2{=\!=}CH—O—R$) also give two bands; one strong band due to asymmetric stretching vibration at about 1220 cm^{-1} and a very weak band due to symmetric stretching at about 850 cm^{-1}. The shift in the asymmetric stretching frequencies in aryl and vinyl ethers to values higher than were found in dialkyl ethers can be explained by resonance. The C—O bond in vinyl alkyl ethers or aryl alkyl is shifted to a higher frequency (1,200–1,275 cm^{-1}) because of double-bond character which strengthens the bond.

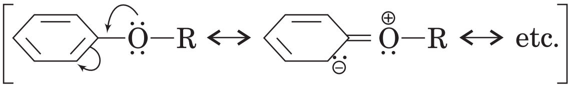


$\bar{\nu}_{C_{sp^2}—O\ str}$: ~1220 cm^{-1}

$R—\ddot{\underset{..}{O}}—R$

No resonance

$\bar{\nu}_{C—O\ str}$: ~1120 cm^{-1}



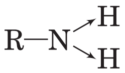
$\bar{\nu}_{C_{sp^2}—O\ str}$: ~1250 cm^{-1}

The value of $\bar{\nu}_{C—O\ str.}$ of a six-membered cyclic ether is same as that of an acyclic ether. However, as the ring becomes smaller, the $\bar{\nu}_{C—O\ str.}$ value moves to lower wave number and this is because the C—O bond strength decreases gradually with increase in angle strain.

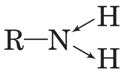
The presence or absence of O—H stretching at 3,200–3,500 cm^{-1} for H-bonded O—H can be used to distinguish between an ether and an isomeric alcohol.

5. Amines

The most important and readily detectable infrared absorptions of primary and secondary amines are the result of N—H stretching vibrations that appear in the region 3,300–3,500 cm^{-1}. Primary amines (R—NH$_2$) show two bands in this region: one caused by symmetric stretching and other by asymmetric stretching. Secondary amines (R$_2$NH) give only one absorption in this region. Tertiary amines (R$_3$N) have no N—H and, therefore, are transparent in this region of infrared spectrum. Hence, it is easy to differentiate among primary, secondary and tertiary amines by inspection of the N—H stretching region.



Symmetric stretching
in 1° amine
$\bar{\nu}_{\text{N—H } str}$: ~3400 cm^{-1}



Asymmetric stretching
in 1° amine
$\bar{\nu}_{\text{N—H } str}$: ~3500 cm^{-1}

The N—H stretching absorptions for aromatic amines are comparatively higher than those of aliphatic amines and this is because the N atom assumes sp^2 state of hybridization and the N—H bond in aromatic compounds are stronger than those in aliphatic compounds.

As with alcohols, the nature of the spectrum of amines depends on the degree of H-bonding. In dilute solution in an inert solvent, the spectra of a primary amine shows two sharp bands at higher frequencies than the bands obtained in the neat (undiluted) liquid amine. However, the shift is somewhat less compared to alcohols because of the weaker H-bonding of amines compared to alcohols.

N—H bending vibrations of 1° amines appear at 1,590–1,650 cm^{-1} and 750–850 cm^{-1} and that of 2° amines appears at about 1,500 cm^{-1}.

The C—N stretching band for aliphatic amines appears in the region between 1,020–1,250 cm^{-1}. Aromatic amines show strong C—N stretching absorption near 1,300 cm^{-1}. The higher frequency is due to the increased force constant as a result of resonance with the benzene ring.

The stretching frequency of N—H bond gives absorption in about the same region where O—H absorbs and thus one may confuse with that of O—H stretching frequency. However, since oxygen is more electronegative than nitrogen, the O—H stretching results in a greater change in bond moment than does N—H stretching. Because of this, one can see that the O—H stretching band is stronger than the N—H stretching band.

6. Carbonyl compounds

The carbonyl group $\left(\gt C{=}O\right)$, which is present in aldehydes ketones, acids, esters, amides, acid chlorides, and anhydrides absorbs strongly in the range from 1,650 to 1,850 cm^{-1} because of its large change in dipole moment. Since the C=O stretching frequency is sensitive to attached atoms, these common functional groups absorb at characteristic frequencies. Figure 4.12 provides the normal base values for the C=O stretching absorption of various functional groups. The C=O stretching frequency of a ketone (approximately in the middle of the range) is usually considered the reference point for comparisons of these values.

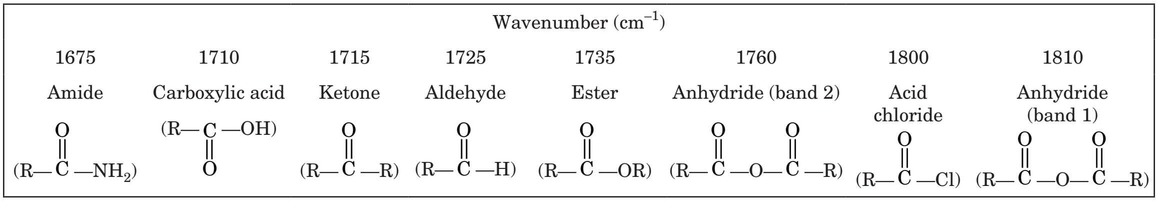
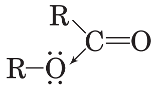
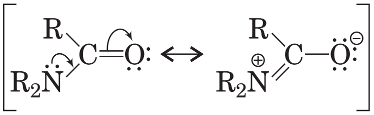

Wavenumber (cm^{-1})
1675
Amide
$(R—\overset{O}{\overset{\|}{C}}—NH_2)$
1710
Carboxylic acid
$(R—\underset{O}{\underset{\|}{C}}—OH)$
1715
Ketone
$(R—\overset{O}{\overset{\|}{C}}—R)$
1725
Aldehyde
$(R—\overset{O}{\overset{\|}{C}}—H)$
1735
Ester
$(R—\overset{O}{\overset{\|}{C}}—OR)$
1760
Anhydride (band 2)
$(R—\overset{O}{\overset{\|}{C}}—O—\overset{O}{\overset{\|}{C}}—R)$
1800
Acid chloride
$(R—\overset{O}{\overset{\|}{C}}—Cl)$
1810
Anhydride (band 1)
$(R—\overset{O}{\overset{\|}{C}}—O—\overset{O}{\overset{\|}{C}}—R)$

Fig. 4.12 Normal base values for C==O stretching frequencies for carbonyl groups

The range of values given in Figure 4.12 can be explained by electron-withdrawing effects (inductive effects), resonance effects, and H-bonding. The first two effects operate in opposite ways to influence the C=O stretching frequency. An electronegative element (e.g., Cl) may tend to draw in the electrons between C and O atoms through its –I effect, so that the C=O bond becomes somewhat stronger. This results in a higher-frequency absorption. Since oxygen is more electronegative than carbon, this effect dominates in an ester to increase the C=O frequency above that of a ketone. A resonance effect may be observed when the unshared pair of electrons on an N atom conjugate with the carbonyl group, resulting in increased single-bond character and a lowering of the C=O stretching frequency. This effect is observed in an amide. The absorption frequency of its C=O group is less than that of a ketone.



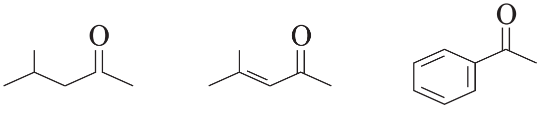
(–I effect of oxygen raises C=O stretching frequency as it predominates over +R effect)



Resonance effect lowers C=O stetching frequency

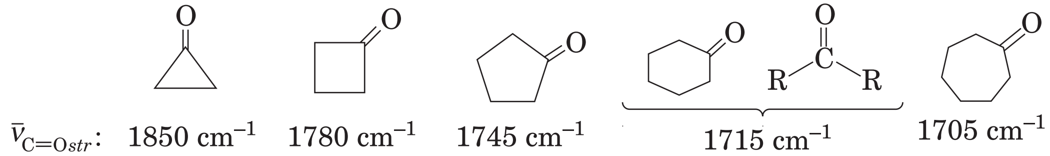
A. Ketones

Ketones show a very strong band for the carbonyl (C=O) group that appears in the range of 1,708–1,720 cm^{-1} for simple aliphatic ketones. Conjugation of the carbonyl group with an α, β-double bond or an aryl group shifts the normal C=O stretching band (~1,715 cm^{-1}) to a lower frequency (1675–1700 cm^{-1}).

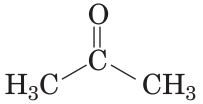


$\bar{\nu}_{C=O\ str}$: ~1717 cm^{-1} ~1690 cm^{-1} ~ 1700 cm^{-1}

The six-membered ring ketone, i.e., cyclohexanone shows the normal frequency for the open chain compounds. However, as the ring becomes smaller in size, the C═O stretching frequency increases progressively. As the ring becomes smaller, the $C—\overset{O}{\overset{\|}{C}}—C$ angle reduces and as a consequence, the *p* character of the ring forming inner orbitals of the carbonyl carbon increases for improving the overlap with other ring-forming orbitals. As a result, the *p* character of the carbon orbital used to form the *σ* bond with oxygen decreases, i.e., *s* character of that orbital increases. Because of this, the stiffness of the C═O bond increases and as a consequence, the stretching frequency increases.

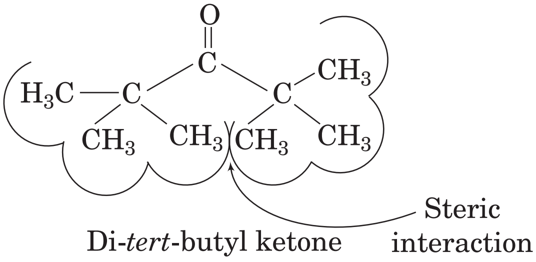


In acyclic ketones, as the branching at *α*-C's increases, the $C—\overset{O}{\overset{\|}{C}}—C$ angle increases (due to steric crowding) and as a consequence, the *p* character of the C—C bond forming orbitals of the carbonyl carbon decreases and because of similar reasoning, the stiffness of the C═O bond decreases to give somewhat lower value of $\bar{\nu}_{C=O\,str.}$



Acetone

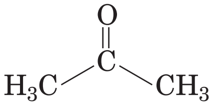
$\nu_{C=O\,str}$: 1715 cm^{-1}



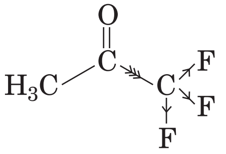
Di-*tert*-butyl ketone

$\nu_{C=O\,str}$: 1697 cm^{-1}

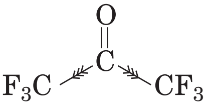
The stretching frequency of the C═O group increases when more and more fluorine atoms are added to the carbons attached to the carbonyl carbon. Thus, compared with the normal value of carbonyl absorption at 1,717 cm^{-1} for acetone, it reaches its maximum in hexafluoroacetone (1,801 cm^{-1}) and is due to the cumulative –I effect of the attached fluorine atoms.



$\nu_{C=O\,str}$: 1717 cm^{-1}

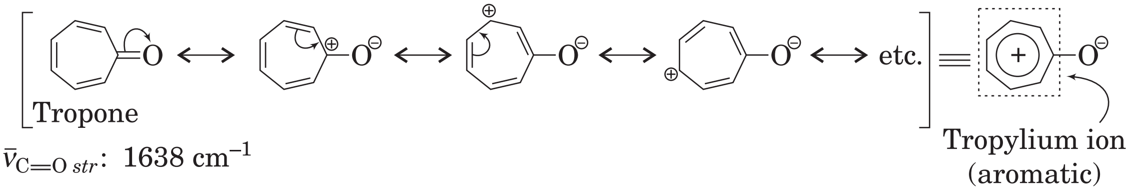


1769 cm^{-1}



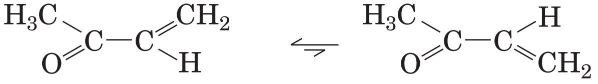
1801 cm^{-1}

Aromaticity may cause lowering of C=O stretching frequency. For example, tropone shows its C=O stretching frequency at 1638 cm^{-1}. Tropone may be considered as a hybrid of a series of dipolar structures which constitute the aromatic 'tropylium ion' system. Because of this, there is considerable weakening of the C=O double bond and lowering of C=O stretching frequency.



$\bar{\nu}_{C=O\ str}$: 1638 cm^{-1}

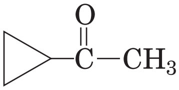
α,β-unsaturated ketones may exit in two conformations, i.e., *s-cis* and *s-trans* and because of this, two carbonyl bands appear in the spectrum. A normal band around 1,720 cm^{-1} and a lower frequency band around 1,685 cm^{-1}. The lower frequency band is due to the *s-trans* conformer, where the electron-delocalization is more effective. Due to repulsive interaction, electron delocalization in *s-cis* conformer is less effective and so its C=O appears at higher frequency. For example, but-3-en-2-one exists as:



s-trans *s-cis*

($\bar{\nu}_{C=O\ str}$: 1685 cm^{-1}) ($\bar{\nu}_{C=O\ str}$: ~1720 cm^{-1})

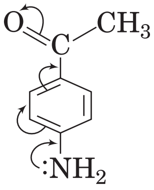
A cyclopropyl ring behaves like a double bond and when attached to C=O, causes lowering of its stretching frequency. For example:



Methyl cyclopropyl ketone

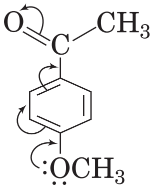
($\bar{\nu}_{C=O\ str}$: 1700 cm^{-1})

In *ortho*- and *para*-substituted aromatic ketones, inductive as well as resonance effect play a significant role in shifting C=O stretching frequency. In *meta*- substituted compounds, the frequency shift is due only to the inductive effect. The C=O stretching frequencies of some *para*-substituted ketones are as follows:



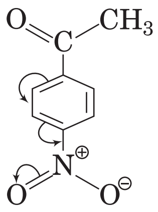
p-Aminoacetophenone

$\bar{\nu}_{C=O\ str}$: 1677 cm^{-1}



p-Methoxyacetophenone

– 1684 cm^{-1}

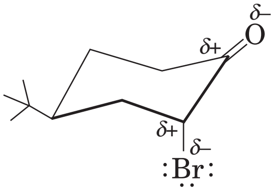


p-Nitroacetophenone

>1684 cm^{-1}

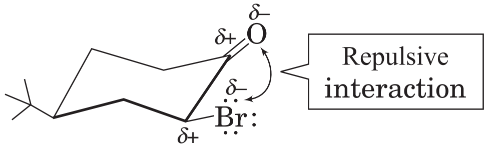
In *p*-aminoacetophenone, the unshared pair of electrons on nitrogen is more available for conjugation (i.e., for resonance interaction with C=O) than the unshared electron pair on the more electronegative oxygen in *p*-methoxyacetophenone and because of this, the first compound exhibits a lower stretching frequency for C=O. Due to strong —R effect of the —NO_2 group, the C=O stretching frequency of *p*-nitroacetophenone increases and in fact the value is somewhat higher than that of *p*-methoxyacetophenone.

Field effect (nonbonded electrostatic interaction) may also lead to shifting of stretching frequency to a higher value. In *α*-halocyclohexanones, the equatorial halogen atom is practically eclipsed with the carbonyl group and so, in this conformation, there operates repulsive interaction between the almost parallel dipole of $\overset{\delta+}{C}-\overset{\delta-}{X}$ and $\overset{\delta+}{C}=\overset{\delta-}{O}$ bonds. As a result of this, the tendency of the C=O group to aquire a partial single bond character decreases. This in turn results in rising of C=O absorption by nearly 15 cm^{-1}. For example:



trans-2-Bromo-4-*tert*-butyl-cyclohexanone

$\bar{\nu}_{C=O\ str}$: 1720 cm^{-1}

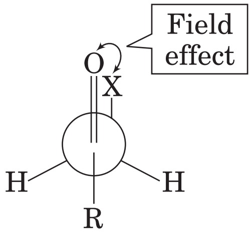


Repulsive interaction

cis-2-Bromo-4-*tert*-butyl-cyclohexanone

$\bar{\nu}_{C=O\ str}$: 1733 cm^{-1}

Due to the same field effect an *α*-haloketone ($RCOCH_2X$) shows two bands is its spectrum. The compound is normally free to adopt several conformations, two of which are shown below:

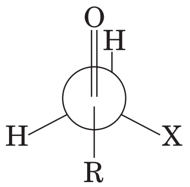


Field effect

cis-form

$\bar{\nu}_{C=O\ str}$: 1740 cm^{-1}

(where X=Br)



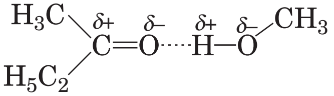
gauche-form

$\bar{\nu}_{C=O\ str}$: 1720 cm^{-1}

(where X=Br)

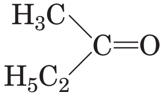
Due to field effect, the C=O stretching bond of the *cis* form appears at a position 20 cm^{-1} higher than that of the *gauche* form where the field effect does not operate.

The C=O stretching absorption band is shifted to lower frequency when the sample is examined in a hydroxylic solvent like methanol. For example, neat sample of ethyl methyl ketone ($CH_3COC_2H_5$) absorbs at 1,715 cm^{-1}, whereas a 10% solution of the ketone in methanol absorbs at 1,706 cm^{-1}. Intermolecular hydrogen bonding between the carbonyl oxygen atom and the —OH group of the solvent decreases the stiffness of the C═O bond.



$\bar{\nu}_{C=O\ str}$: 1706 cm^{-1}

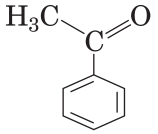
(10% methanol solution)



$\bar{\nu}_{C=O\ str}$: 1715 cm^{-1}

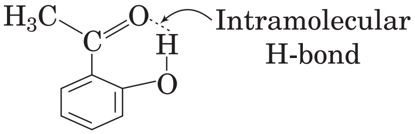
(pure sample)

Intramolecular H-bonding is another factor which lowers the C═O stretching frequency by about 50 cm^{-1}. This lowering is, however, dependent on the strength of the hydrogen bond. *o*-Hydroxyacetophenone, for example, shows its C═O stretching at a much lower frequency as compared to acetophenone.



Acetophenone

$\bar{\nu}_{C=O\ str}$: 1680 cm^{-1}

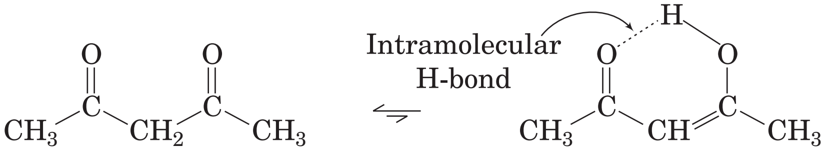


o-Hydroxyacetophenone

$\bar{\nu}_{C=O\ str}$: 1634 cm^{-1}

β-Diketones exhibit tautomerization and exist as equilibrium mixture of enol and keto tautomers. Since many *β*-diketones contain large amounts of the enol forms, carbonyl peaks for both the enol and keto tautomers may be observed. For example:

Acetyl acetone:



Keto-form

C═O doublet

Enol-form

$\bar{\nu}_{C=O\ str}$: 1723 cm^{-1} (symmetric)

$\bar{\gamma}_{C=O\ str}$: 1706 cm^{-1} (asymmetric)

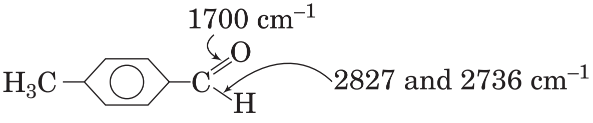
$\bar{\gamma}_{C=O\ str}$: 1622 cm^{-1} (hydrogen bonded)

$\bar{\nu}_{O-H\ str}$: 2400–32 cm^{-1} (hydrogen bonded)

The C═O group in the enol form appearing at about 1,622 cm^{-1} is substantially shifted and intensified in comparison to the normal ketone value, 1,715 cm^{-1}. The shift is a result of internal hydrogen bonding and resonance.

B. Aldehydes

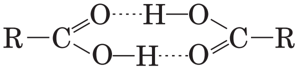
The carbonyl groups of aldehydes absorb at slightly higher frequency than that of the corresponding methyl ketones. Aliphatic aldehydes (RCHO) absorb between 1,725 and 1,740 cm^{-1} and this carbonyl absorption responds to the structural changes in the same manner as ketones. Aldehydes can be distinguished from ketones by means of aldehydic C—H stretching for which two moderately intense bands one near 2,850 cm^{-1} and other near 2,750 cm^{-1} appear. The appearance of these two bands is attributed to Fermi resonance between the fundamental aldehyde C—H stretching and the first overtone of the aldehydic C—H bending vibration. The band near 2,850 cm is frequently not observed in the case of saturated aliphatic aldehydes because of overlapping by the strong saturated C—H absorption in the same region. In the case of aromatic aldehydes two bands are observed frequently. *p*-Tolualdehyde, for example, shows two bands (doublet) for aldehydic C—H stretching at 2,827 and 2,736 cm^{-1}.



p-Tolualdehyde

C. Carboxylic Acids

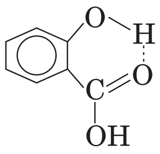
A carboxylic acid exists in monomeric form only in very dilute solution, and its C=O stretching frequency is 1,760 cm^{-1} because of the electron-withdrawing effect of oxygen. However, acids in concentrated solution, in the form of neat liquid or in the solid state tend to dinerize via hydrogen bonding. This dimerization weakens the C=O bond and results in lowering the stretching frequency of saturated acids to the range of 1,700–1,730 cm^{-1} (same as that for the C=O group of aldehydes and ketones).



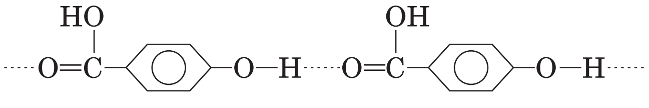
(dimeric form)

Because of intermolecular H-bonding the C=O band is usually broad. The band is shifted to lower frequencies with conjugation to a C=C or phenyl group. The other infrared absorption characteristic of a carboxyl group is a very broad band for O—H stretching in the region 2,400–3,400 cm^{-1}. This band usually centres near 3,000 cm^{-1} and partially obscures the C—H stretching bands. If a very broad O—H stretch band is seen only with a C=O band, it almost certainly indicates that the compound is a carboxylic acid.

Intramolecular hydrogen bonding reduces the frequency of C=O stretching absorption to a greater degree than does intermolecular H-bonding. For example, salicylic acid absorbs at 1,665 cm^{-1}, whereas *p*-hydroxybenzoic acid absorbs at 1,680 cm^{-1}.



Salicylic acid
(Intramolecular H-bonding)
$\bar{\nu}_{C=O\ str}$: 1665 cm^{-1}

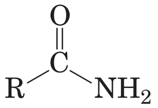


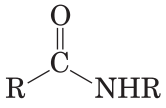
p-Hydroxybenzoic acid
(Intermolecular H-bonding)
$\bar{\nu}_{C=O\ str}$: 1680 cm^{-1}

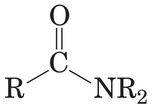
Three other bands arising from C—O stretching, O—H in-plane bending and O—H out-of-plane bending appear at 1,210–1,320, 1,395–1,440 and near 920 cm^{-1}, respectively in the spectrum of dimeric carboxylic acids.

D. Amides

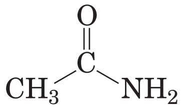
Amides show a very strong band for the C═O group that appears in the range 1,640–1,700 cm^{-1} (pure sample when hydrogen bonding is maximum). On dilution of the sample with a nonhydrogen bonding solvent, the extent of hydrogen bonding decreases and the C═O absorption is shifted to a higher frequency around 1,690 cm^{-1}. The carbonyl absorption of tertiary amides is, however independent of its physical state as there is no H-bonding occurs in this case.


Primary amide

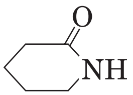

Secondary amide


Tertiary amide

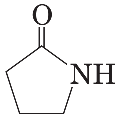
Cyclic amides (lactamss) give the expected increase in C═O stretching frequency for decreasing ring size.


Acetamide

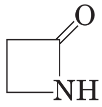
$\bar{\nu}_{C=O\ str}$: 1,680 cm^{-1}


δ-Valerolactam

$\bar{\nu}_{C=O\ str}$: 1,670 cm^{-1}

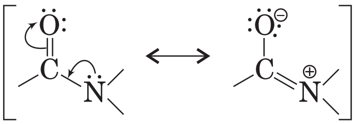

γ-Butyrolactam

$\bar{\nu}_{C=O\ str}$: 1,700 cm^{-1}


β-Propiolactam

$\bar{\nu}_{C=O\ str}$: 1,745 cm^{-1}

It has been already mentioned that the low absorption frequency of C═O relative to the keto carbonyl is due to effective resonance interaction.


(+R > –I)

A pair of fairly strong N—H stretching band appears at about 3,180 and 3,350 cm^{-1} for a primary amide in the solid state. The 3,180 and 3,350 cm^{-1} bands result from the symmetric and asymmetric stretching vibrations, respectively. In the solid state, secondary amides and lactams show one band at about 3,300 cm^{-1}.

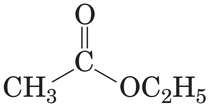
The band due to N—H bending of primary amides appears in the region 1,620–1,640 cm^{-1}. This band for secondary amides appears in the region 1515–1570 cm^{-1}. Primary and secondary amides also give a very broad band due to out-of-plane N—H bonding absorption in the region 600–750 cm^{-1}.

Primary amides display medium intensity C—N stretching vibrations near 1400 cm^{-1}.

E. Esters

The two most characteristic features in the spectrum of a normal ester are the strong C═O band, which appears in the range from 1,735 to 1,750 cm^{-1}, and C—O band, which appears in the range from 1,000 to 1,300 cm^{-1}. In an ester, the –I effect of the alkoxy (—OR) group predominates over its +R effect and so, the C═O stretching band appears in a region of higher frequency compared to that of a ketone. The C═O stretching vibrations are shifted by about 15–25 cm^{-1} to lower frequencies with *α,β*-unsaturation or aryl substitution (conjugation effects).

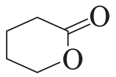
The C═O stretching frequency in lactones (cyclic esters) increases gradually with decreasing ring size.



$CH_3-\overset{\overset{O}{\|}}{C}-OC_2H_5$

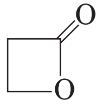
Ethyl acetate

$\bar{\nu}_{C=O\ str}$: 1735 cm^{-1}



δ-Valerolactone

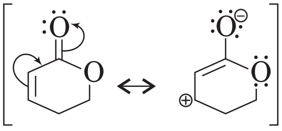
1770 cm^{-1}



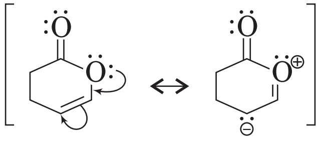
β-Propiolactone

1820 cm^{-1}

Unsaturation *α* to the C═O group reduces the C═O stretching frequency, but unsaturation *α* to the single-bonded oxygen increases it. For example:



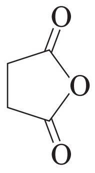
$\bar{\nu}_{C=O\ str}$: 1725 cm^{-1}



$\bar{\nu}_{C=O\ str}$: 1760 cm^{-1}

F. Anhydrides

Anhydrides show two strong bands for the C═O groups. Simple noncyclic and saturated anhydrides generally give bands near 1,750 and 1,820 cm^{-1}. The two bands result from symmetric and asymmetric stretch. Anhydrides and acid chlorides are the two common functional groups that have a C═O band appearing at such a high frequency. Conjugation moves the absorption to a lower frequency and ring strain (cyclic anhydrides) moves the absorption to a higher frequency. For example:



Succinic anhydride

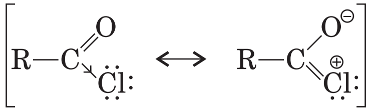
$\bar{\nu}_{C=O\ str}$: 1865 and 1782 cm^{-1}

The higher frequency band is more intense in acyclic (for unstrained cyclic) anhydrides, while the lower frequency band is more intense in strained cyclic anhydrides. This feature can be used to distinguish between acyclic and cyclic anhydrides.

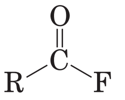
All acid anhydrides display their C—O stretching as one or two strong bands in the region 900–1,300 cm^{-1}.

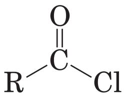
G. Acid halides

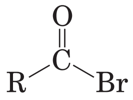
The characteristic spectral feature of an acid halide is a very strong and high frequency band for the C═O group which appears in the range of 1,770–1,870 cm^{-1}. The high frequency C═O absorption in acid halides may be due to the high electronegativity of halogen that makes it hard for the oxygen to draw electrons and consequently weakens the resonance (–I > +R).



Much less effective resonance







$\bar{\nu}_{C=O\ str}$: ~1870 cm^{-1} ~1800 cm^{-1} ~1800 cm^{-1}

Some aromatic acid chlorides (ArCOCl) display another rather strong band on the lower frequency side of the C═O band. In benzoyl chloride (PhCOCl), this band appears at about 1,730 cm^{-1}. It is probably a Fermi resonance band originating from an interaction of the C═O vibration, with an overtone of a strong band for aryl-C stretching appearing in the range from 800 to 900 cm^{-1}. In acid chlorides C—Cl absorption bands appear in the range from 550 to 730 cm^{-1}.

7. Nitriles

The C≡N group in a nitrile gives a medium-intensity, sharp band in the region 2,110 to 2,270 cm^{-1}. Aliphatic nitriles (RCN) absorb at about 2,250 cm^{-1}, whereas their aromatic counterparts (ArCN) absorb at lower frequencies, near 2,230 cm^{-1} because of conjugation of the triple bond with the ring.

4.3.6 Infrared Correlation Table

For analysing infrared spectra of an unknown compound, one must be familiar with the frequencies at which various functional groups absorb and for this, infrared correlation tables must be consulted. A simplified correlation table (Table 4.7) is given below. Absorption intensities are referred to as strong (s), medium (m), and weak (w).

Bond	Type of Vibration	Frequency (cm^{-1})	Intensity
C—H	Alkenes (stretching)	2,850–3,000	s
	—CH_3 (bending)	1,375	m
	—CH_2— (bending)	1,465	m
	Alkenes (stretching)	3,000–3,100	m
	(out-of-plane bending)	650–1,000	s

	Aromatics (stretching)	3,050–3,150	s
	(out-of-plane bending)	690–900	s
	Alkynes (stretching)	3,300	s
	Aldehydes	2,800–2,900	w
		2,700–2,800	w
C═C	Alkenes	1,600–1,680	m—w
	Aromatics	1,475 and 1,600	m—w
C≡C	Alkynes	2,100–2,250	m—w
C═O	Aldehydes	1,725–1,740	s
	Ketones	1,705–1,720	s
	Carboxylic acid	1,700–1,730	s
	Esters	1,735–1,750	s
	Amides	1,640–1,700	s
	Anhydrides	1,750 and 1,820	s
	Acid chlorides	1,800	s
C—O	Alcohols, ethers, esters, carboxylic acids, anhydrides	1,000–1,300	s
O—H	Alcohols and phenols		
	Free	3,600–3,650	m
	H-bonded	3,200–3,400	m
	Carboxylic acids	2,400–3,400	m
N—H	1° and 2° amines and amides		
	(stretching)	3,100–3,500	m
	(bending)	1,550–1,640	m—s
C—N	Amines	1,000–1,350	m—s
C≡N	Nitriles	2,240–2,260	m
N═O	Nitro (RNO$_2$)	1,350 and 1,550	s
C—X	Fluorides	1,000–1,400	s
	Chlorides	540–785	s
	Bromides and iodides	<667	s

SOLVED PROBLEMS

1. When does a molecule absorb infrared radiation?

Solution Covalent bonds are not static. They are more like springs with weights on each end. When two atoms are bonded to each other, the bond stretches back and forth. Bonds can also bend when three or more atoms are joined together. These bond stretching and bending vibrations represents the different vibrational modes. Absorption of IR light may cause changes in the vibrational energy levels of a molecule. However, absorption of infrared light quantum can occur only if the dipole moment of the molecule is different in the two vibrational levels. The variation of dipole moment with the change in interatomic distance during vibration corresponds to an oscillating electric field that can interact with the oscillating electric field associated with the electromagnetic radiation and when the frequency of one field matches with that of the other, absorption occurs. These vibrations absorb infrared radiation at certain quantized frequency. The absorption is maximum when the frequencies of these two oscillating electric fields become identical. When a molecule is exposed to infrared radiation of that frequency, energy is absorbed and the amplitude of that vibration is increased.

2. Is it possible to distinguish a pair of enantiomers by IR spectroscopy?

Solution It is not possible to distinguish a pair of enantiomers by IR spectroscopy.

3. What do you mean by fundamental vibrations and overtones?

Solution The fundamental absorptions correspond to the frequency of the first vibrational transition from the zeroth vibrational level to the first, v_0 to v_1. The term overtone is used to apply to any integral multiple of a given fundamental frequency. The transition from $v_0 \rightarrow v_2$ or $v_0 \rightarrow v_3$ are the first and second overtones of the fundamental and require radiation of twice and three times of its frequency. If the fundamental frequency is $\bar{v}$, the overtone bands appear at $2\bar{v}, 3\bar{v},$ etc.

4. What do you mean by combination band, difference band and Fermi resonance?

Solution When two vibrational frequencies $(\bar{v}_1 \text{ and } \bar{v}_2)$ in a molecule couple to give rise to a vibration of a new frequency within the molecule, and when such a vibration is IR active, it is called a combination band. This band is actually the sum of the two interacting band $(\bar{v}_{\text{comb}} = \bar{v}_1 + \bar{v}_2)$.

The observed frequency that results from the difference between the two interacting bands is called a difference band $(\bar{v}_{\text{diff}} = \bar{v}_1 - \bar{v}_2)$.

When a fundamental vibration couples with an overtone or combination band, the coupled vibration is called *Fermi resonance*.

5. Calculate the vibrational degrees of freedom in the following molecules:

(a) H_2O (b) C_2H_2 (c) C_6H_6 (d) $CHCl_3$

Solution

(a) H_2O is a non-linear molecule. For such molecules, vibrational degrees of freedom $= 3n - 6$ (where n = total number of atoms in the molecule). Here, $n = 3$.

$\therefore$ Number of vibrational degrees of freedom (fundamental vibrational modes) $= 3 \times 3 - 6 = 3$

(b) Acetylene (H—C≡C—H) is a linear molecule. For such molecules, vibrational degrees of freedom $= 3n - 5$ (where n = total number of atoms in the molecule). Here, $n = 4$.

Therefore, the number of vibrational degrees of freedom $= 3 \times 4 - 5 = 7$

(c) Benzene (C_6H_6) is a nonlinear molecule. Here, $n = 12$. Therefore, the number of vibrational degrees of freedom $= (3 \times 12 - 6) = 30$.

(d) Chloroform ($CHCl_3$) is a non-linear molecule. Here, $n = 5$. Therefore, the number of vibrational degrees of freedom = $(3 \times 5 - 6) = 9$.

6. ***cis*-1,2-Dichloroethylene is IR active with respect to $\bar{\nu}_{C=C}$, whereas *trans*-1,2-dichloroethylene is not. Explain.**

Solution Due to stretching of C═C bond, change of dipole moment takes place in *cis*-1,2-dichloroethylene, but not in *trans*-1,2-dichloroethylene. It is for this reason, infrared absorption occurs in the case of *cis*-isomer, but not in the case of *trans*-isomer and therefore, the *cis*-isomer is IR active with respect to $\bar{\nu}_{C=C}$, whereas the *trans*-isomer is not.

7. **Hydrogen bonding may change the position of IR absorption. Illustrate with an example.**

Solution Hydrogen bonding brings about a considerable downward shift in the wave number of absorption. For example, alcohol in the vapour state (isolated molecule) shows O—H stretching at about 3,600 cm^{-1}. However, in the liquid state (in associated form), a broad absorption bond appears at 3,200 cm^{-1}.

8. **How can you distinguish between the two types of hydrogen bonding (intramolecular and intermolecular) by IR spectroscopy?**

Solution It can be easily done by taking IR spectra of a given compound at two different concentrations. If there is a shift in the absorption position of a particular band, then the type of hydrogen bonding in the substance is intermolecular otherwise it is intramolecular. Intramolecule hydrogen bonding is independent upon the concentration of the solution.

9. **What happens to O—H stretching frequency when 20 ml of CCl_4 is added to 4 ml of pure ethanol?**

Solution Due to intermolecular hydrogen bonding, the O—H absorption bond in ethanol appears at 3,200 cm^{-1}. When carbon tetrachloride is added to it, hydrogen bonding becomes weak due to dilution and as a result, the absorption position is raised.

10. **In acetylene, C_{sp}—H stretching appears at about 3300 cm^{-1}. How can it be distinguished from an O—H stretching in alcohol?**

Solution In alcohol, the O—H *str* absorption band appears in the range 3,200–3,600 cm^{-1}. The band is broad and changes its position with change in concentration. On the other hand the C_{sp}—H stretching absorption band is sharp and is concentration independent. Therefore, these two absorptions can be easily distinguished.

11. **How might the following pairs of isomers be distinguished from their IR absorption spectra?**
(a) $PhCH_2COCH_3$ and $PhCOCH_2CH_3$; (b) $PhCOCH_2CH_3$ and $PhCH_2CH_2CHO$; (c) $PhCOOCH_3$ and CH_3COOPh; (d) $CH_3COCH_2COCH_2CH_3$ and $CH_3COCH_2CH_2COCH_3$; (e) *p*-$H_2NC_6H_4CH_2COOH$ and *p*-$H_2NCH_2C_6H_4COOH$

Solution

(a) The phenyl group is adjacent to C═O in propiophenone ($PhCOCH_2CH_3$) but not in phenylacetone ($PhCH_2COCH_3$). Because of this, the C═O *str* band for the former ketone will appear at lower frequency than the latter.

(b) The C═O stretching frequency of the aldehyde (3-phenylpropanal) is higher than that of the ketone (propiophenone). Also, the aldehyde C—H *str* band near 2,800 cm^{-1} will characterize the former.

(c) The C═O *str* band for methyl benzoate (PhCOOMe) appears at ~1,720 cm^{-1} (the C═O group of the ester is conjugated with the benzene ring) and the band for phenyl acetate (CH_3COOPh) appears at ~1,770 cm^{-1} (the —O-group of the ester is conjugated with benzene ring).

(d) Since 2,4-hexadione ($CH_3COCH_2COCH_2CH_3$) is a *β*-diketone, it will be highly enolic. Because of this, its IR spectrum will show broad O—H *str* bond and a C═O *str* bond appearing at very low frequency. The IR spectrum of 2,5-hexadione ($CH_3COCH_2CH_2COCH_3$) will be similar to that of a simple dialkyl ketone.

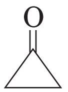
(e) Because of resonance interaction of the unshared pair of electrons on nitrogen with the ring *π* electrons, the aryl amino groups are much less basic than alkyl amino groups, and, in general, they do not undergo protonation to yield zwitterions. Thus, while 4-amiophenylacetic acid shows the separate characteristics of both —NH_2 and —COOH groups (N—H *str* band at 3300 cm^{-1}; a broad O—H *str* band in the region 2,500–3,500 cm^{-1} and a C═O *str* band near 1,700 cm^{-1}). The —NH_2 group in 4-(aminomethylbenzoic acid ($H_2NCH_2C_6H_4COOH$) is relatively more basic, and so, the compound exists as a zwitterion. Because of this, it shows the characteristic C$\overset{\cdots}{=}$O *str* bands near 1,600 cm^{-1}.

12. Explain why methanol is a good solvent for UV but not for IR spectroscopy.

Solution Methanol (CH_3OH) does not absorb in UV region, i.e., it is transparent above 200 mμ. But it absorbs strongly in the infrared region (4,000 cm^{-1} to 650 cm^{-1}). It is for this reason methanol is a good solvent for UV but not for IR spectroscopy.

13. How will you distinguish between the two compounds in each of the following pairs?

(a)



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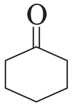
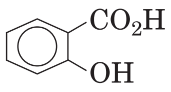


(b)



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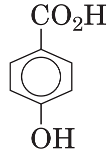
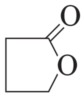


(c)



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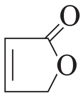


Solution

(a) In cyclic ketones C═O *str* frequency increases as the size of the ring decreases (ring strain increases). Thus, cyclopropanone shows absorption at higher wave number (nearly 1,850 cm^{-1}), whereas cyclohexanone absorbs at nearly 1,715 cm^{-1} (the same wave number at which saturated acyclic ketones absorb).

(b) In *o*-hydroxybenzoic acid (salicylic acid), intramolecular hydrogen bonding occurs and so, the absorption band due to C═O *str* appears at nearly 1,665 cm^{-1} and also, its position in the spectrum is concentration independent. However, in *p*-hydroxybenzoic acid, the molecules remain associated through intermolecular hydrogen bonding and the C═O absorption band appear at about 1,680 cm^{-1}. The position of absorption is raised when the solution is diluted by adding a non-aqueous solvent like carbon tetrachloride.

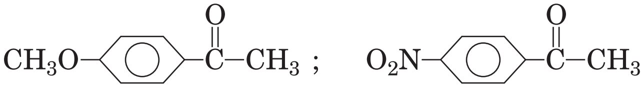
(c) The C═O *str* absorption of the conjugated lactone occurs at a lower frequency of 1,750 cm^{-1} (resonance interaction with the double bond causes decrease in force constant) compared to the saturated lactone (1,770 cm^{-1}).

14. Which of the following diatomic molecules are IR inactive (do not absorb in the IR region)?

Cl_2, H—Br, I—Cl, D_2, O_2

Solution Cl_2, D_2 and O_2 are homodiatomic molecules. Their stretching vibrations are not accompanied by any change in dipole moment, and for this reason, they do not absorb in the infrared region, i.e., they are IR inactive.

15. How can the following two compounds be distinguished?



I II

Solution Due to +R-effect of the —OCH_3 group, the bond order (force constant) of C═O decreases and this results in lowering of absorption frequency. On the other hand, due to –R effect of the —NO_2 group, the bond order of C═O increases and this results in absorption at a higher frequency (>1,700 cm^{-1}).

16. The C—H *str* band in $CHCl_3$ appears at 3000 cm^{-1}. If the force constant of C—H is identical to that of C—D, calculate the C—D *str* frequency in $CDCl_3$.

Solution

$$\bar{v} = \frac{1}{2\pi C}\sqrt{\frac{K}{\mu}}$$

for C—H $\mu = \dfrac{m_1 m_2}{m_1 + m_2} = \dfrac{12 \times 1}{12 + 1} = \dfrac{12}{13} = 0.92$

for C—D $\mu = \dfrac{12 \times 2}{12 + 2} = \dfrac{24}{14} = 1.71$

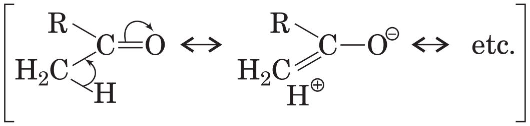
Since the force constant *K* is the same, we can write:

$$\frac{\bar{v}_{C—D}}{\bar{v}_{C—H}} = \sqrt{\frac{\mu_{C—H}}{\mu_{C—D}}} = \sqrt{\frac{0.92}{1.71}} = 0.73$$

Therefore, the C—D *str* absorption band will appear at 3,000 × 0.73 = 2,190 cm^{-1}.

17. Explain why the C═O *str* frequency of an aldehyde (RCHO) is slightly higher than that of the corresponding methyl ketone ($RCOCH_3$).

Solution In the methyl ketone ($RCOCH_3$), the —CH_3 group donates electron by its +I effect and hyperconjugation. As a result, the bond order of the carbonyl group somewhat decreases, and so, C═O *str* frequency decreases. That's why the C═O *str* frequency of an aldehyde is slightly higher than that of the corresponding methyl ketone.



Hyperconjugation in methyl ketone

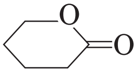
18. Arrange the following bonds in decreasing order of vibrational frequency: C—Br, C—C, C—Cl, C—O, C—H, C—I

Solution As the atom bonded to carbon increases in mass the factor μ (reduced mass) in the following equation increases and consequently, the frequency decreases.

$$\bar{\nu} = \frac{1}{2\pi C}\sqrt{\frac{K}{\mu}}$$

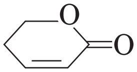
Therefore, the decreasing order of vibrtional frequency is: C—H > C—C > C—O > C—Cl > C—Br > C—I.

19. Explain the C═O *str* frequency values of the following lactones.



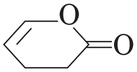
I

(1,735 cm^{-1})



II

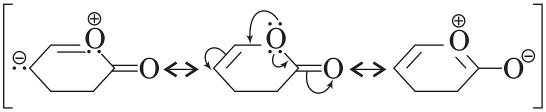
(1,725 cm^{-1})



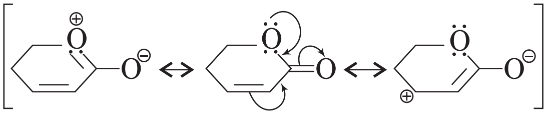
III

(1,760 cm^{-1})

Solution In lactone III, conjugation of the carbon–carbon double bond with the oxygen *p* orbital diminishes the normal resonance interaction of that oxygen with the carbonyl group resulting in an increase in the double bond character of the carbonyl group. As a consequence, an increase in C═O *str* frequency occurs as compared to the saturated lactone I. On the other hand, in lactone II, the carbonyl group is involved in resonance interaction with the double bond. This results in a decrease in double-bond character of the carbonyl group. Consequently, a decrease in C═O *str* frequency occurs as compared to the saturated lactone I.



III



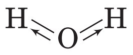
II

20. What characteristic of vibrational frequencies makes infrared spectroscopy useful in determining structures of organic compounds?

Solution The various vibrational absorption frequencies are specific for a given functional group or alkyl group (i.e., —$CHMe_2$) regardless of its bonding environment. For example, the C═O *str* frequency of cyclic ketones changes with ring size but is the same for different cyclic ketones with the same ring size.

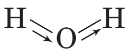
21. How many types of vibration are possible for H_2O molecule? Explain with required figures.

Solution The non-linear H_2O molecule have three vibrational degrees of freedom and they may be depicted as follows:



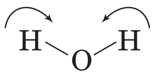
Symmetric stretching

$\bar{\nu}_{O—H\ str}$: 3,652 cm^{-1}



Asymmetric stretching

$\bar{\nu}_{O—H\ str}$: 3,756 cm^{-1}



Bending (scissoring)

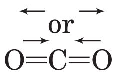
$\bar{\nu}_{O—H\ def}$: 1,596 cm^{-1}

(Other bending modes such as rocking, wagging, and twisting are not considered because these do not change the shape of the molecule.)

22. How many fundamental vibrational frequencies would you expect to observe in the infrared spectrum of carbon dioxide (CO_2)?

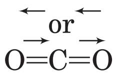
Solution CO_2 is a linear molecule. Therefore, four [(3*n* – 5) = 3 × 3 – 5 = 4] fundamental vibrational modes are expected for this molecule. These are as follows:

(a)



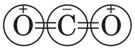
Symmetric stretching
(IR inactive)

(b)



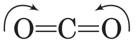
Asymmetric stretching
(IR active)
$\bar{\nu}_{C=O\ str}$: 2,350 cm^{-1}

(c)



Out-of-plane binding
[+ and – signs represent vibrations perpendicular to the plane of the paper]

(d)



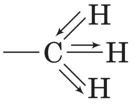
In-plane bending

These two are equivalent and appear at 667 cm^{-1}

The symmetric stretching vibration (a) is IR inactive because it produces no change in dipole moment of the molecule. The asymmetric stretching vibration (b) is IR active. The bending vibrations (c) and (d) are equivalent and they have the same frequency and are said to be doubly degenerate. Thus, two bands (at 2,350 cm^{-1} and 667 cm^{-1}) are expected to be present in the infrared spectrum of carbon dioxide.

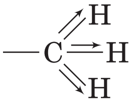
23. Show all the C—H vibrational modes of a —CH_3 group and give their $\bar{\nu}_{\text{C—H}\,str}$ and $\bar{\nu}_{\text{C—H}\,def}$ values.

Solution In a methyl group, the C—H vibrational modes are coupled and two distinct bands appear at 2,962 and 2,872 cm^{-1}. The first of these results from asymmetric stretching mode in which two C—H bonds of the —CH_3 group are extending while the third one is contracting. The second arises from symmetrical stretching in which all the three C—H bonds extend and contract in phase.



Asymmetric stretching

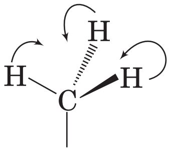
$\bar{\nu}_{\text{C—H}\,str}$: 2,962 cm^{-1}



Symmetric stretching

$\bar{\nu}_{\text{C—H}\,str}$: 2,872 cm^{-1}

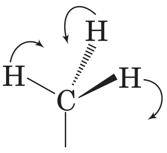
Two C—H bending vibrations occur within the methyl group. The first of these is the symmetrical bending vibration which appears at 1,375 cm^{-1} and involves in-phase bending of the C—H bonds (I). The second one is the asymmetric bending vibration which appears at 1450 cm^{-1} and involves out-of-plane bending of the C—H bonds (II).



I

Symmetric bending

$\bar{\nu}_{\text{C—H}\,def}$: 1,375 cm^{-1}



II

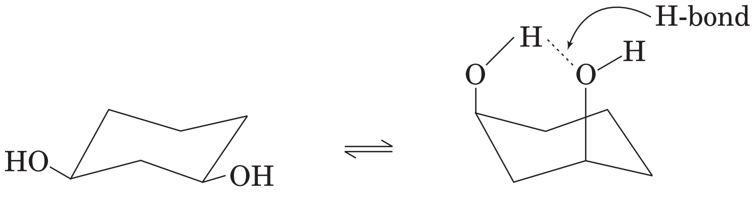
Asymmetric bending

$\bar{\nu}_{\text{C—H}\,def}$: 1,450 cm^{-1}

In I, the C—H bonds are moving like the closing petals of a flower and in II, one petal opens and two petals close.

24. From the IR spectral studies how would you establish that *cis*-cyclohexane-1,3-diol exists mainly in the diaxial conformation?

Solution *cis*-Cyclohexane-1,3-diol may exist in two conformations as shown below:

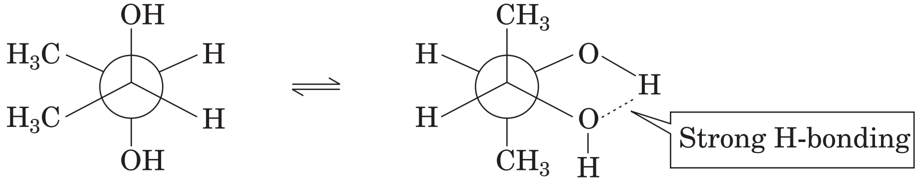


(diequatorial conformation) (diaxial conformation)

When the solution of the compound in carbon tetrachloride is diluted gradually, no change in O—H *str* frequency is indicated. This observation, therefore, suggests that the compound mainly exists in diaxial conformation in which the two —OH groups are involved in intramolecular H-bonding.

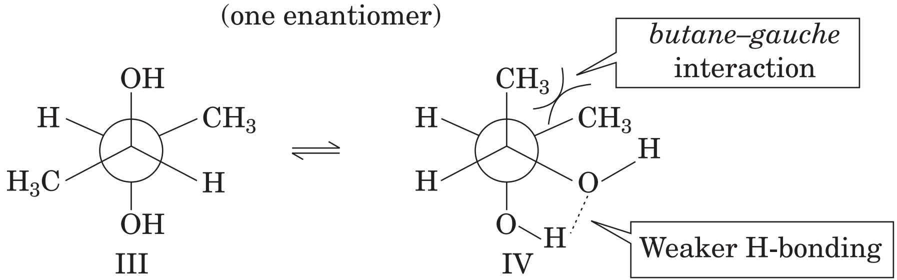
25. How can the *threo*(active)-isomer of butane-2,3-diol be distinguished from its *erythro*(*meso*)-isomer by infrared spectroscopy?

Solution Each of the *threo* and *erythro* isomers of butane-2,3-diol may exist in two conformations of which one is intramolecularly hydrogen bonded.



I II

threo-Butane-2,3-diol
(one enantiomer)



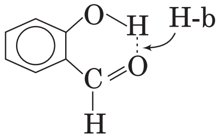
III IV

erythro-Butane-2,3-diol
(*meso*)

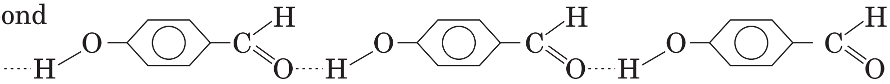
Because of *butane–gauche* interaction, the internal H-bonding in IV is weaker than in II. The more the H-bonding is strong, the more the O—H *str* frequency is lower and the more the difference of stretching of free O—H and H-bonded O—H is higher. So, in the case of the *threo*-isomer, the difference is expected to be higher than in the case of the erythro-isomer. In fact, $\Delta\bar{\nu}$ for *threo* is 49 cm^{-1} and for *erythro* is 42 cm^{-1}. Therefore, by analyzing the O—H stretching absorption bands in the infrared spectrum of the dilute solutions of these two diastereoisomers, one can detect them. (However, the analysis requires high-resolution technology.)

26. How would you distinguish salicylaldehyde from *p*-hydroxybenzaldehyde by analysing their infrared spectrum?

Solution Since *p*-hydroxybenzaldehyde molecules remain associated through intermolecular H-bonding, its O—H stretching frequency (a broad band at 3550 cm^{-1}) will shift nearly 100 cm^{-1} higher wave number (a sharp band at 3650 cm^{-1}) on dilution in CCl_4 and this is because on dilution the O—H bond becomes free from H-bonding effect. However, in salicylaldehyde intramolecular H-bonding (chelation) occurs and because of this, the position and the nature of O—H stretching absorption band will remain same in the spectrum of both the pure sample and its dilute solution in CCl_4. Hence, by these observations salicylaldehyde may easily be distinguished from *p*-hydroxybenzaldehyde.



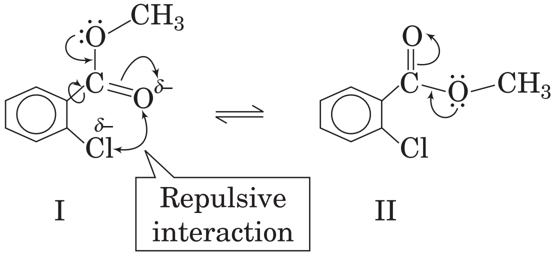
Salicylaldehyde
(no change of O—H *str*
frequency on dilution)



p-Hydroxybenzaldehyde
(on dilution O—H *str* frequency changes)

27. Esters of *o*-chlorobenzoic acid show two C═O *str* frequencies. Explain.

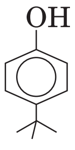
Solution An ester of *o*-chlorobenzoic acid may exist in the following two rotamers (I and II):



I II

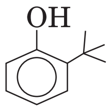
Due to the field effect caused by the *ortho* Cl atom, the C═O *str* frequency in I shifts to a higher value. No such effect operates in the rotamer II. For this reason, esters of *o*-chlorobenzoic acid show two C═O stretching frequencies.

28. In the following three substituted phenols, the O—H *str* bands appear at 3,608 cm^{-1} in I, at 3,605 and 3,643 cm^{-1} in II and 3,643 cm^{-1} in III. Explain these observations.



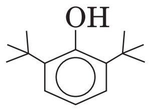
I

($\bar{\nu}_{\text{O—H}\ str}$: 3,608 cm^{-1})



II

($\bar{\nu}_{\text{O—H}\ str}$: 3,605 and 3,643 cm^{-1})



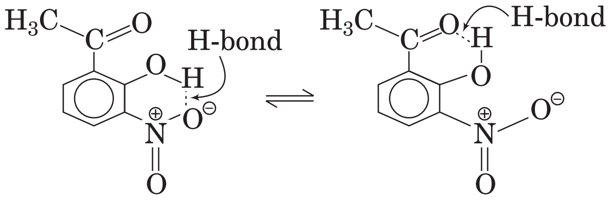
III

($\bar{\nu}_{\text{O—H}\ str}$: 3,643 cm^{-1})

Solution In *p*-*tert*-butylphenol (I), only a single O—H *str* band appears at 3608 cm^{-1} because the molecules remain associated through intermolecular hydrogen bond. In the *o*-isomer (II), two bands are seen at 3,605 and 3,643 cm^{-1}; this is because in some molecules there is association, whereas in others the O—H group is not H-bonded due to steric crowding caused by the *t*-butyl group. In 2,6-di-*tert*-butyl phenol (III), only a single O—H *str* band appears at 3,643 cm^{-1}. This is because two molecules cannot approach close enough to form intermolecular hydrogen bond.

29. 2-Hydroxy-3-nitroacetophenone shows two C═O stretching frequencies at 1692 and 1658 cm^{-1} respectively. Explain.

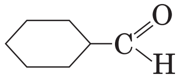
Solution Due to formation of two types of intramolecular hydrogen bonding, 2-hydroxy-3-nitroacetophenone exists as equilibrium mixture of two forms (I and II) as shown below:



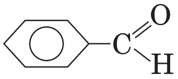
I II

The form I with free carbonyl group shows the normal conjugated C═O stretching frequency. However in the form II, the C═O stretching frequency is shifted to a lower value due to intramolecular H-bonding with the —OH group. For this reason, 2-hydroxy-3-nitroacetophenone shows two C═O stretching frequencies at 1,692 and 1,658 cm^{-1}, respectively, for I and II.

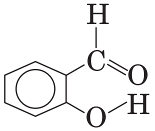
30. Predict the frequency shift of carbonyl absorption in the following aldehydes:



I



II

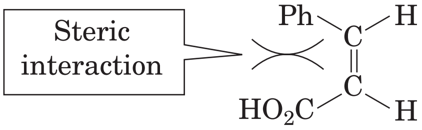


III

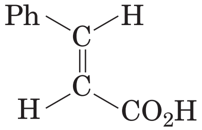
Solution Cyclohexane carbaldehyde I, being saturated will absorb at about 1,730 cm^{-1}. In benzaldehyde II, the absorption will be shifted to lower frequency (1,700 cm^{-1}) due to conjugation. In salicylaldehyde III, intramolecular hydrogen bonding (chelation) causes a further large frequency shift to around 1,666 cm^{-1}.

31. *cis*-Cinnamic acid absorbs at a higher frequency than its *trans*-isomer. Explain.

Solution



cis-Cinnamic acid



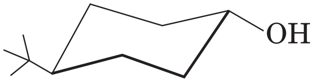
trans-Cinnamic acid

$\bar{\nu}_{C=O\ str}$: 1,705 cm^{-1} 1,680 cm^{-1}

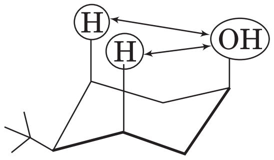
In the *cis*-isomer, the two bulky substituents (—Ph and —COOH groups) are placed on the same side of the C══C bond. Due to steric interaction, the C══O moiety of the —COOH group goes out of the plane of double bond. As a result, conjugation is reduced and C═O stretching frequency shifts to a higher value. On the other hand, the conjugative effect is more pronounced in the *trans*-isomer in which the two bulky groups are on the opposite sides of the double bond. As a consequence, the double-bond character of the carboxyl C═O group in the *trans*-acid is reduced and so, it absorbs at relatively lower frequency (1,680 cm^{-1}).

32. How would you distinguish *cis*-4-*tert*-butylcyclohexanol from its *trans*-isomer by infrared spectroscopy?

Solution Axial and equatorial substituents on a cyclohexane ring show different ring-to-substituent stretching frequencies. An equatorial substituent usually absorbs at a higher frequency than does the same substituent in the axial position and this is due to 1,3-di-axial interaction (steric interaction). Due to presence of the very bulky *tert*-butyl group (in the equatorial position), the ring is rigid and cannot flip. Therefore, the diastereoisomer which shows a C—O *str* band at ~1,060 cm^{-1} is the *trans*-4-*tert*-butylcyclohexanol (—OH is in equatorial position) and the diastereoisomer which shows a C—O *str* bond at ~950 cm^{-1} is the *cis*-isomer (—OH is in axial position).



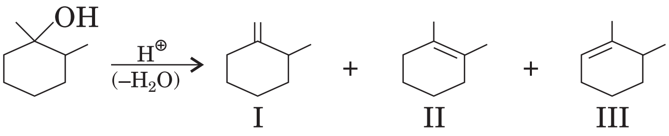
trans-4-*tert*-Butyl
-cyclohexanol
$\bar{\nu}_{\text{C—O (e)}}$: –1,060 cm^{-1}



cis-4-*tert*-Butyl
-cyclohexanol
$\bar{\nu}_{\text{C—O (a)}}$: ~950 cm^{-1}

33. Acid-catalyzed dehydration of 1,2-dimethylcyclohexanol (*cis* or *trans*) can give three alkenes. Write their structures and explain how IR spectral studies can differentiate among them.

Solution

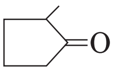
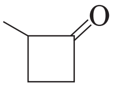


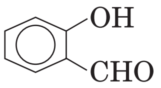
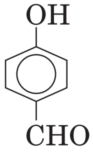
The three products can easily be differentiated by C—H out-of-plane bending absorptions in the region 800–1,000 cm^{-1}. The alkene I with a terminal methylene group will absorb at 885–895 cm^{-1}. The alkene II, being a symmetrical tetrasubstituted alkene, will show no absorption in this' region and the alkene III, being a trisubstituted alkene, will absorb at 790–840 cm^{-1}.

34. Compare the C═O stretching frequencies of acetone and hexamethylacetone and explain. [CU 2010]

Solution See **article no. 4.3.5.**

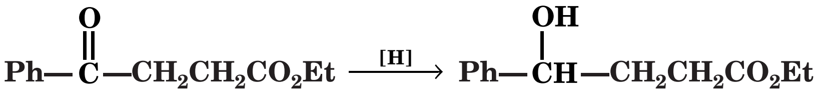
35. How can you distinguish the following molecules by IR-spectroscopy? **[CU 2010]**

(a)  and 

(b)  and 

Solution See **article no. 4.3.5** and **solved problem no. 2.6.**

36. How IR spectroscopy can be used to study the progress of the following transformations? **[CU 2014]**

(a) 

$$\text{Ph}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{CH}_2\text{CH}_2\text{CO}_2\text{Et}\xrightarrow{[\text{H}]}\text{Ph}-\overset{\overset{\text{OH}}{|}}{\text{C}}\text{H}-\text{CH}_2\text{CH}_2\text{CO}_2\text{Et}$$

(b) $\mathbf{PhCH{=}NR \xrightarrow{[H]} PhCH_2NHR}$

Solution

(a) In $PhCOCH_2CH_2CO_2Et$, the band due to C=O *str* appears in the range 1,680–1,700 cm^{-1} (because of conjugation with Ph). Reduction of this ketone produces a secondary alcohol which absorbs at 3,300 cm^{-1} due to O—H *str*. With progress of the reaction the C=O *str* bond gradually disappears and the O—H *str* band gradually appears. When the reaction is completed, the band due to C=O *str* completely disappears and only the O—H *str* band appears in the spectrum.

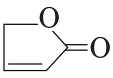
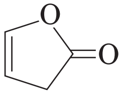
(b) With progress of the reaction the band due to C=N *str* in the region 1,640–1,690 cm^{-1} gradually disappears and the band due to N—H *str* in the range 3,300–3,500 cm^{-1} gradually appears. On completion of the reaction, the first band vanishes and the second band becomes prominent (but the band is very weak). Also, a band due to C—N stretching absorption appears in the region 1,000 to 1,350 cm^{-1}.

37. Discuss the effect of dilution by carbon tetrachloride on IR absorption position of O—H stretching of ethanol. **[CU 2016]**

Solution When the spectrum of a concentrated solution of ethanol is taken, a broad band at lower frequency (~3,330 cm^{-1}) appears due to O—H *str* (hydrogen bonded). However, when the solution is much diluted with carbon tetrachloride, intermolecular H-bonding becomes very weak and a sharp band appears in the region 3,500–3,700 cm^{-1}.

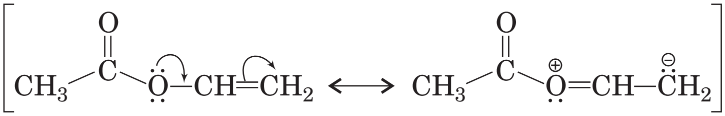
38. How would you distinguish between the members of the following pairs by IR spectroscopy? **[CU 2017]**

(a) Vinyl acetate and methyl acrylate

(b)  and 

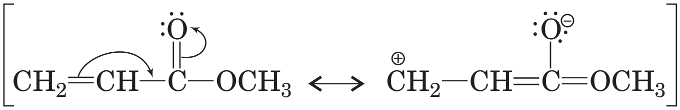
Solution

(a) Conjugation involving the single-bonded oxygen shifts the C=O vibrations to higher frequencies and this is because the resonance interaction of oxygen with C=O is reduced as it involved in another resonance.



Vinyl acetate

In the spectrum of vinyl acetate, the C=O band appears at 1,762 cm^{-1}, which is 25 cm^{-1} higher than the normal ester. On the other hand, the C=O band in methylacrylate appears at 1,725 cm^{-1} (10 cm^{-1} lower than the normal ester) due to resonance interaction of the double bond with C=O.



Methyl acrylate

(b) See **article no. 4.3.5.**

39. How would you distinguish between the members of each of the following pairs by IR spectroscopy? [CU 2018]

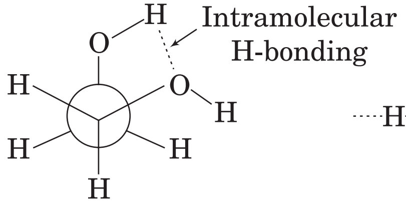
(a) Vinyl acetate and methyl acrylate

(b) Ethanol and ethylene glycol

Solution

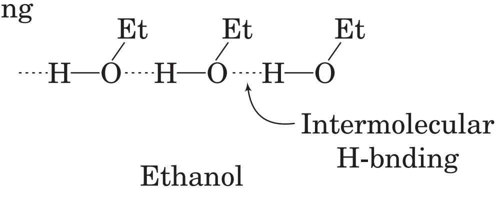
(a) See the answer to **Problem no. 38**.

(b) Because of intramolecular H-bonding, the O—H *str* frequency of ethylene glycol ($HOCH_2CH_2OH$) does not change with change in concentration. However, the O—H *str* frequency of ethanol (CH_3CH_2OH) changes with change in concentration and this is because dilution makes intermolecular H-bonding weak and causes shifting of O—H *str* band to higher frequency.



Ethylene glycol

$\bar{\nu}_{O—H\,str}$: ~3,200 cm^{-1}



Ethanol

$\bar{\nu}_{O—H\,str}$: 3,300–3,400 cm^{-1}

40. Why the C≡C *str* of acetylene is IR inactive? [CU 2017]

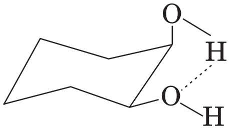
Solution See **article no. 4.3.1.2**.

41. How can you differentiate the following pair by applying IR spectroscopy? Methyl bezoate; Phenyl acetate

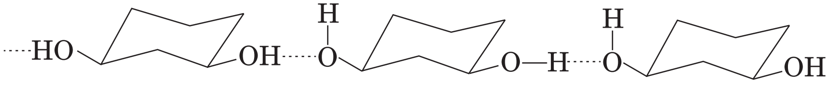
Solution See **solved problem no. 11**.

42. How will you distinguish *cis*-1,2-cyclohexanediol and *cis*-1,3-cyclohexanediol by IR spectroscopy? [CU 2015]

Solution Intramolecular H-bonding occurs in *cis*-1,2-cyclohexanediol. On the other hand, the molecules of *cis*-1,3-cyclohexanediol remain associated through intermolecular H-bonding. Dilution with non-associative and inert solvent like CCl_4 causes shifting of O—H *str* frequency to a higher value in *cis*-1,3-cyclohexanediol, whereas the O—H *str* frequency of *cis*-1,2-cyclohexanediol is concentration independent.



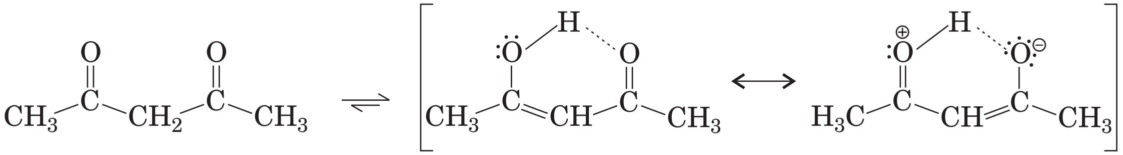
cis-1,2-Cyclohexanediol
(intramolecular H-bonding)
$\bar{\nu}_{\text{O—H } str}$: ~3,597 cm^{-1}



cis-1,3-Cyclohexanediol
(intermolecular H-bonding)
$\bar{\nu}_{\text{O—H } str}$: ~3,618 cm^{-1}

43. Comment on the infrared spectral behaviour of acetylacetone ($CH_3COCH_2COCH_3$).

Solution Acetylacetone (a *β*-diketone) exhibit tautomerization and exists as an equilibrium mixture of keto and enol tautomers of which the enol form predominates (64%).



Keto form

Enol form

$\bar{\nu}_{\text{C=O } str}$: 1,723 cm^{-1} (symmetric *str*)
1,706 cm^{-1} (asymmetric *str*)
(appears as a doublet)

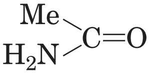
$\bar{\nu}_{\text{C=O } str \text{ (H-bonded)}}$: 1,622 cm^{-1}
$\bar{\nu}_{\text{O—H } str \text{ (H-bonded)}}$: 2,700–3,200 cm^{-1}

In the enol form, the C═O *str* bond is shifted to lower frequency (1,622 cm^{-1}) due to intramolecular H-bonding and conjugation. A weak and broad O—H *str* absorption band also appears in the region 2,700–3,200 cm^{-1}.

Since the keto form is also present, a doublet of the symmetric and asymmetric stretching frequencies is found to be present for the two C═O groups. Relative intensities of the enol and keto carbonyl absorptions depends on the relative amount of the tautomers present at equilibrium.

STUDY PROBLEMS

1. The C—H stretching band in an alkane appears at ~2,900 cm^{-1} in the IR spectrum. What wavelength does this correspond to? Calculate the energy change involved.
[**Hint:** $\lambda = 1/\nu = 1/2{,}900\ cm^{-1} = 3.45 \times 10^{-4}\ cm^{-1} = 3.45\ \mu m$.]
2. Some of the fundamental vibrations are IR active while the others are not. Explain.
3. Unlike propane and propyne, ethylene and ethyne have no carbon to carbon multiple bond stretching bands. Explain.
4. The C—H *str* band of an alkene appears at 2,900 cm^{-1}. Predict the value of the corresponding C—D frequencies where H is replaced by D.
[**Hint:** $\bar{\nu}_{C—D} = 0.73\,\bar{\nu}_{C—H}$]
5. How will you distinguish between maleic acid and fumaric acid by using IR spectroscopy?
6. How would you distinguish between the compounds in each pair by infrared spectral studies?
   (a) Methyl benzoate and phenylacetate
   (b) δ-valerolactone and δ-valerolactum
   (c) Ethylbenzene and *o*-xylene
   (d) Acetaldehyde and acetone
   (e) Salicyclic acid and *p*-hydroxybenzoic acid
7. Which of the following compounds has the highest C═O stretching frequency? Give your reasoning.



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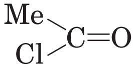

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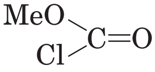

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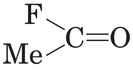

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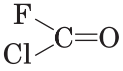
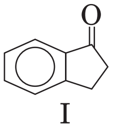


V

8. How would you distinguish between the following two compounds by IR spectral analysis?



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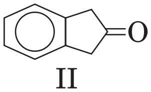
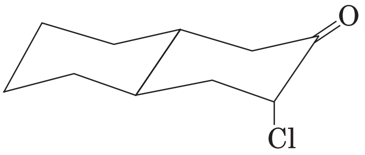
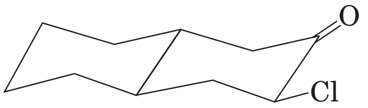
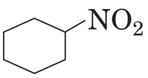
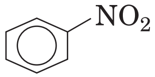
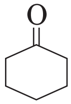
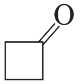


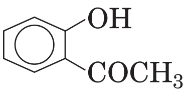
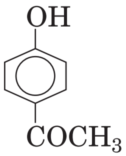
II

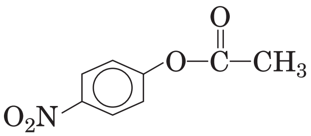
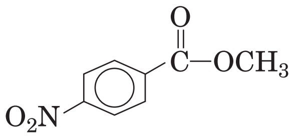
9. The carbonyl absorption of the carboxylate ion differ considerably from that of the parent acid. Explain.
[**Hint:** Due to resonance, the two carbon-oxygen bonds are of equivalent strength, intermediate between C═O and C—O.
Two bands, one due to asymmetric stretching (near 1,600 cm^{-1}) and the other due to symmetric stretching (near 1,400 cm^{-1}) are expected to be found in the case of carboxylate ion.]

10. How would you distinguish between the compounds in each pair on the basis of IR spectroscopy?

(a)  and 

(b)  and  (c)  and 

(d)  and 

(e)  and 

(f) $CH_3COOCH{=}CH_2$ and $CH_2{=}CH{-}COOCH_3$

11. How will you classify primary, secondary and tertiary alcohols using infrared spectral studies?

12. Arrange the following compounds in order of increasing C=O stretching frequency and give your reasoning.

CH_3CONH_2; CH_3CHO; CH_3COCH_3; $CH_3COOC_2H_5$; CH_3COCl

13. How can you distinguish among pentane, 1-pentene and 1-pentyne on the basis of infrared spectroscopy.

14. Dehydrochlorination (E2) of 2,3-dimethyl-2-chlorobutane produces two alkenes. How would you differentiate them by IR spectral analysis?
[**Hint:** One of the products is IR inactive. The other display C=C *str* absorption at 1640 cm^{-1} and C—H out-of-plane bending absorption at 890 cm^{-1}.]

15. The IR spectrum of benzalacetone ($PhCH{=}CHCOCH_3$) in CS_2 at room temperature shows two separate bands for C=O stretching vibration. Explain this observation.

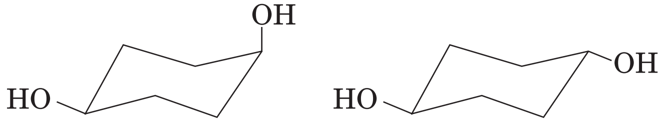
16. Which of the following vibrational modes will show no absorption band?

(a) symmetric $N{\equiv}C{-}C{\equiv}N$ stretch (b) asymmetric CO_2 stretch
(c) symmetric O=C=S stretch, and (d) symmetric CO_2 stretch

17. IR absorption due to carbonyl stretching occurs at higher frequencies than stretching of the carbon-carbon double bond. Explain.

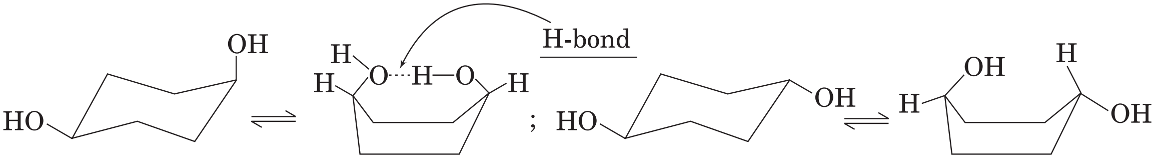
18. How can you differentiate 1°, 2°, and 3° amines by IR spectroscopy?

19. How can you differentiate between the following two isomeric compounds by infrared spectral studies?



cis *trans*

[**Hint:**



cis *trans*

The *trans*-isomer will give a sharp band near 3,600 cm^{-1} but the *cis*-isomer will give a broad band for O—H *str* at around 3,300 cm^{-1} (due to intramolecular H-bonding) along with another band around 3,600 cm^{-1} (for free O—H).]

20. Acetophenone reacts with hydroxyl amine to yield two isomeric oximes. Both of them are separately subjected to Beckmann rearrangement. Identify the products on the basis of infrared spectral studies.

21. How can you differentiate between the following two isomeric diketones on the basis of infrared spectroscopy?

$Me_2CHCOCH_2COMe$; $MeCOCMe_2COMe$

22. The hydrolysis of an ester RCOOR′ in dilute aqueous KOH produces the alcohol (R′OH) and the potassium salt of the carboxylic acid (RCOOK). How can the progress of hydrolysis be followed by infrared spectroscopy?

[**Hint:** The disappearance of the ester C═O *str* band near 1,720 cm^{-1} is to be followed. The reaction product shows the carboxylate absorptions near 1,600 cm^{-1} and 1,350 cm^{-1}.]

23. How can IR spectroscopy be used to distinguish the members of the following pairs?

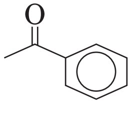
(a) 1-Hexyne and 3-hexyne

(b) *cis*-3-Hexene and *trans*-3-hexene

(c) Natural rubber (*cis*-polyisoprene) and butyl rubber (polyisobutene)

[**Hint:** (a) Both the C≡C *str* and C_{sp}—H *str* bands are expected to be found in the spectrum of 1-hexyne but not in the spectrum of 3-hexyne. (b) The out-of-plane C—H *def* bands for *cis* and *trans* alkenes are expected to appear respectively near 970 and 700 cm^{-1}. (c) Natural rubber contains an alkene group but butyl rubber does not. Therefore, the former can be identified by the pressure of a weak/medium band for C═C stretching.]

24. Arrange the following compounds in order of increasing C═O stretching frequency and give your reasoning.



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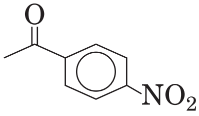

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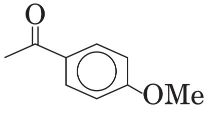

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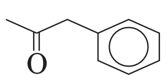

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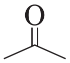


V

25. How infrared spectral analysis could help in distinguishing the following pairs?

(a) p—$H_2NCH_2C_6H_4CO_2H$ and p—$H_2NC_6H_4CH_2CO_2H$

(b) $CH_3CH_2CH_2CONH_2$ and $CH_3CH_2CONHCH_3$

26. Explain the exceptionally low C═O *str* frequency in 2,4,6-cycloheptatrienone.

4.4 NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Introduction

Nuclear magnetic resonance (NMR) is a spectroscopic method which is, in fact, more important to organic chemists than IR spectroscopy. Felix Bloch and Edward Purcell, both of the United States, detected first in 1946 the phenomenon of nuclear magnetic resonance and in 1952 they shared the Nobel Prize for physics. Nuclear magnetic resonance (NMR) is concerned with the magnetic properties of certain atomic nuclear, notably the nucleus of the hydrogen atom (the proton) and that of the carbon-13 isotope of carbon. Whereas IR spectroscopy reveals the types of functional groups present in a molecule, NMR gives information about the number of magnetically distinct atoms of the type being studied. When hydrogen nuclei (protons) are studied, for instance, we can determine the number of each of the distinct types of hydrogen nuclei and at the same time we obtain information regarding the nature of the environment of each type in the molecule. The ^1H nucleus is by far the most commonly studied by NMR spectroscopy because of its high natural abundance (99.98%) and presence in the majority of organic compounds. In this section, we actually concentrate on absorption of radio frequency radiation by nuclei and the resulting transition between energy levels.

4.4.1 Nuclear Spin States

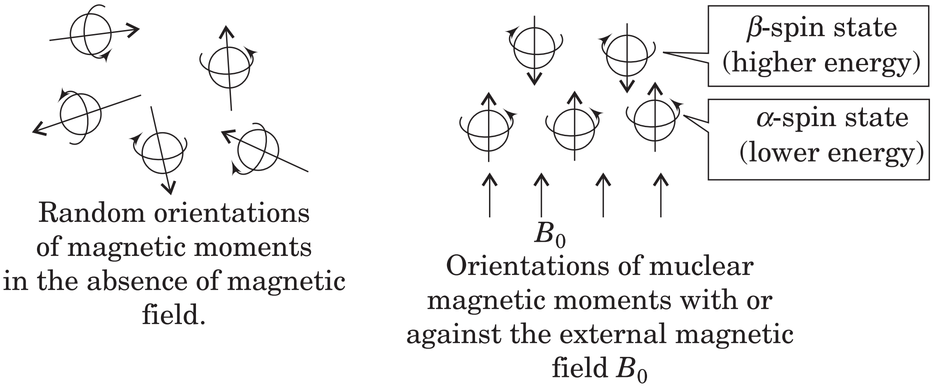
Any atomic nucleus that has an odd mass number, an odd atomic number, or both has a property called *spin*, i.e., it has a quantized spin angular momentum and a resulting nuclear magnetic moment. The allowed nuclear spin states are determined by the spin quantum number I, of the nucleus. A nucleus with spin quantum number I has $2I + 1$ spin states. A proton (^1H) has the spin quantum number $I = \frac{1}{2}$ and has two allowed spin states $\left[2 \times \left(\frac{1}{2}\right) + 1 = 2\right]$ for its nucleus: $-\frac{1}{2}$ and $+\frac{1}{2}$. Spin quantum numbers and allowed nuclear spin states of the nuclei of some elements common to organic compounds are shown in Table 4.8. *To exhibit NMR phenomenon nuclei must have their spin quantum number I greater than zero.*

Table 4.8 Spin quantum numbers and allowed nuclear spin states of some common nuclei

Element	Atomic number	Mass number	Nuclear spin quantum number (I)	Number of spin states ($2I + 1$)	NMR activity
$^{1}_{1}H$	Odd	Odd	1/2	2	Active
$^{2}_{1}H$	Odd	Even	1	3	Active
$^{12}_{6}C$	Even	Even	0	0	Inactive
$^{13}_{6}C$	Even	Odd	1/2	2	Active
$^{14}_{7}N$	Odd	Even	1	3	Active
$^{15}_{7}N$	Odd	Odd	1/2	2	Active
$^{16}_{8}O$	Even	Even	0	0	Inactive
$^{17}_{8}O$	Even	Odd	5/2	6	Active
$^{10}_{5}B$	Odd	Even	3	7	Active
$^{11}_{5}B$	Odd	Odd	3/2	4	Active
$^{19}_{9}F$	Odd	Odd	1/2	2	Active
$^{31}_{15}P$	Odd	Odd	1/2	2	Active
$^{34}_{16}S$	Even	Even	0	0	Inactive
$^{35}_{17}Cl$	Odd	Odd	3/2	4	Active

4.4.2 Orientation of Nuclear Spins in an Applied Magnetic Field

Like any spinning charged body, the nucleus of hydrogen atom (the proton) behaves like a tiny spinning bar magnet and generates a magnetic field. The magnetic moments of protons are oriented in random fashion in field-free space. But, when a proton is placed in a uniform magnetic field, its magnetic moment, according to quantum mechanics, can assume only certain discrete orientations and the system is then said to be quantized. A proton $\left(I = \frac{1}{2}\right)$ may have two possible orientations, i.e., it may either remain align with the field $\left[\text{the lower energy } \alpha\text{-spin state } \left(\text{spin } + \frac{1}{2}\right)\right]$ or against the field $\left[\text{the higher energy } \beta\text{-spin state } \left(\text{spin } - \frac{1}{2}\right)\right]$. We can also describe these orientations as parallel with or antiparallel with the applied field. Certain quantum of energy must be needed to cause the proton to flip over from the lower to the higher energy state. Orientations of magnetic moments generated by spinning nuclei in absence and presence of external magnetic field are shown in Figure 4.11.



Random orientations of magnetic moments in the absence of magnetic field.

Orientations of muclear magnetic moments with or against the external magnetic field B_0

Figure 4.11 Orientations of nuclear magnetic moments in absence and presence of external magnetic field

4.4.3 Theory of Nuclear Magnetic Resonance

The energy difference between the proton in α- and β-spin states is very small and out of one million nuclei only about ten more are in the lower (α-spin) than in the higher energy (β-spin) state at 25°C. The energy needed to flip the proton, in an NMR spectrometer is supplied by electromagnetic radiation in the radio frequency region. Since the nucleus is spinning, its rotational axis draws out a circle perpendicular to the applied field. This motion of the nucleus is called *precession*. An example of this type of gyroscopic motion is a common top, which precesses when spun with an initial axis of rotation different from the earth's gravitational field. This precessional frequency, i.e., the angular frequency ω (which is also termed as *Larmor frequency*) must be exactly equal to the frequency of the electromagnetic radiation (ν) necessary to induce a transition from one spin state to another and when this happens, i.e., when $\nu = \omega$, the nucleus and the radiofrequency beam are said to be *in resonance* (hence the term *nuclear magnetic resonance*) and only then absorption of energy by the nucleus occurs. This may be shown by Figure 4.12.

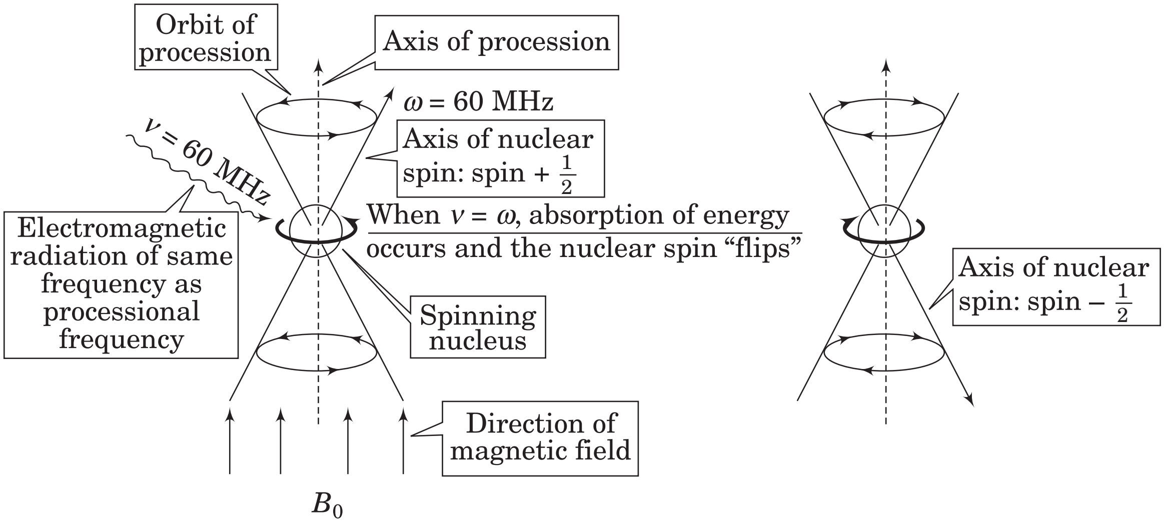
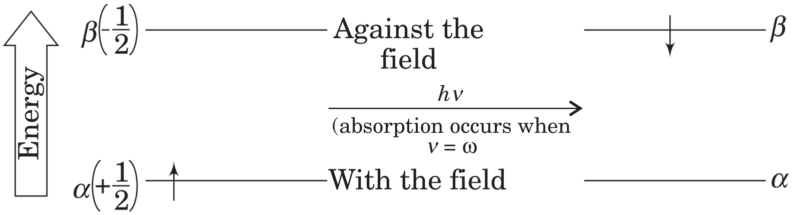

Orbit of procession
Axis of procession
$\omega = 60$ MHz
$\nu = 60$ MHz
Axis of nuclear spin: spin + $\frac{1}{2}$
Electromagnetic radiation of same frequency as processional frequency
When $\nu = \omega$, absorption of energy occurs and the nuclear spin "flips"
Spinning nucleus
Axis of nuclear spin: spin – $\frac{1}{2}$
Direction of magnetic field
B_0

Figure 4.12 The nuclear magnetic resonance process; absorption of electromagnetic radiation with subsequent spin 'flip' occurs when the frequency of radiation (ν) is equation to the frequency of precession (ω).

The process may also be represented by the following simplified diagram:



Just how much energy is needed to flip the proton over depends on the strength of the applied field. The stronger the field, the greater the tendency to remain lined up with it and higher the frequency of radiation needed to do the job. The spin-state energy separation as a function of the strength of the applied magnetic filed B_0 is shown in Figure 4.13.

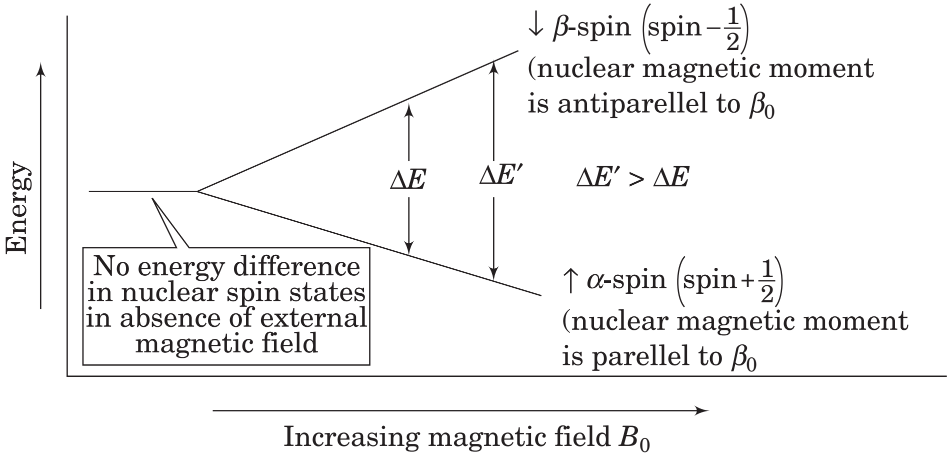


Figure 4.13 The spin-state energy separation as a function of the strength of the applied magnetic field, B_0.

In an applied magnetic field, a magnetic nucleus like proton precess at a frequency ν, which is proportional to the strength of the applied field. The exact frequency is given by:

$$\nu = \frac{\gamma B_0}{2\pi}, \text{ i.e., } \nu \propto B_0$$

where B_0 = strength of the applied external magnetic field experienced by the proton,
γ = gyromagnetic ratio (the ratio between the nuclear magnetic moment, μ, and the nuclear magnetic momentum, I.

Thus, the precessional frequency, which is equal to the frequency of radiation required for resonance, depends on the strength of the applied field and isotope being studied. For example, if a proton is placed at an external magnetic field of 1.4 Tesla (i.e., 14,000 Gauss), it will precess at 60 million cycles per second, and the corresponding precessional frequency would be ν = 60 MHz. Similarly, under an external magnetic field of 2.3 Tesla, the frequency would be 100 MHz, and so on.

Some typical values (approx.) for ν are given in Table 4.9 for selected values of field strength B_0, for some common magnetic nuclei.

Table 4.9 Frequencies (in MHz) and field strengths at which selected nuclei have their nuclear resonances

B_0/Tesla	1.4	1.9	2.3	4.7	7.1	11.7	14.1
Nucleus							
$^{1}_{1}$H	60	80	100	200	300	500	600
$^{2}_{1}$H	9.2	12.3	15.3	30.6	46.0	76.8	92
$^{11}_{5}$B	19.2	25.6	32.0	64.2	96.9	159.8	192
$^{13}_{6}$C	15.1	20.1	25.1	50.3	75.5	125.7	151
$^{14}_{7}$N	4.3	5.7	7.2	14.5	21.7	36.1	43
$^{17}_{8}$O	8.1	10.8	13.6	27.1	40.7	67.8	81
$^{19}_{9}$F	56.5	75.3	94.1	188.2	288.2	470.5	565

In principle, we could place a substance in a magnetic field of constant strength and then obtain a spectrum in the same way we obtain an IR or a UV spectrum, i.e., by passing radiation of steadily changing frequency through the substance and observing the frequency at which radiation is absorbed. In practice, however, it has been found more convenient to keep the radiation frequency constant and to vary the strength of the magnetic field. The majority of low-cost NMR spectrometers use this mode (*field sweep*). However, in modern instruments called *pulsed Fourier transform (FT) spectrometers*, the magnetic field is held constant and an rf pulse of short duration excites all the protons simultaneously. Since the rf pulse covers a range of frequencies (all the frequencies over the ^{1}H range, for example, spread around 100 MHz at 2.3 T, etc.), therefore each nucleus can absorb the frequency it requires to come into resonance (flip its spin) and produce a signal. The NMR spectrum produced in this case is called **Fourier Transform NMR (FT-NMR)** *spectrum* which can be recorded in 2 seconds. Also, a large number of FID (Free Induction Decay) signals can be averaged in a few minutes using less than 5 mg of the sample.

Shielding causes different hydrogens to exhibit signals at different frequencies: We have already seen that the frequency of an NMR signal depends on the strength of the magnetic field sensed by the nucleus (Figure 4.13). Therefore, if all the protons in a compound were to experience the same magnetic field, they would all give signals of the same frequency. If this mere the case, the NMR spectrum of each compound would consist of a single signal that would tell us nothing about the structure of the compound (except that it contains hydrogens).

In fact, all hydrogens do not experience the same magnetic field. In a magnetic field, the electrons circulate about the proton and induce a local magnetic field (B_{local}) that opposes the applied magnetic field (B_0) and, therefore, subtracts from it. As a consequence, the amount of magnetic field that the nuclei actually experiences through the surrounding electrons, i.e., the **effective magnetic field** (B_{eff}), in somewhat smaller than the applied magnetic field.

$$B_{\text{eff}} = B_0 - B_{\text{local}} \; [B_{\text{local}} = \sigma B_0, \text{ where } \sigma \text{ is the shielding parameter}]$$

This relation indicates that the more the electron density there is near a proton, the more the proton is shielded from the applied magnetic field and the greater is B_{local}. The shielding of this type is known as *diamagnetic shielding*.

Therefore, protons in electron-rich environments (in the presence of electropositive groups) experience a *smaller effective magnetic field*. Since ΔE is then smaller, they require a *lower frequency* to come into resonance, i.e., to flip their spin. On the other hand, protons in electron-poor environments (in the presence of electronegative groups) experience a *larger effective magnetic field* and because of larger ΔE, they require a *higher frequency* to come into resonance.

An NMR spectrum exhibits a signal for each proton in a different electronic environment. More shielded protons in electron-rich environments appear at lower frequencies (on the right-hand side of the spectrum), whereas less shielded (or deshielded) protons in electron-poor environments appear at higher frequencies (on the left-hand side of the spectrum). This becomes clear from Figure 4.14.

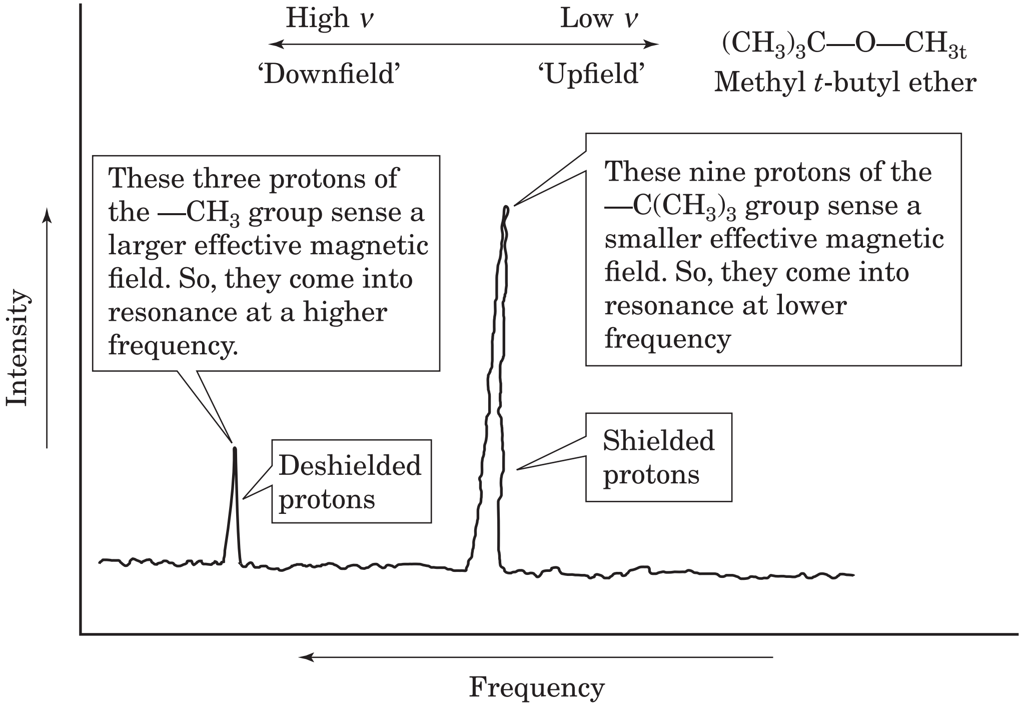


Figure 4.14 $^1_1$HNMR spectrum of methyl *t*-butyl ether which shows shielded protons come into resonance at lower frequencies than deshielded protons.

The terms *upfield* and *downfield* actually come into use when CWNMR spectrometers (operating on field sweep) were used (before the emergence of FTNMR spectrometers) and become very much entrenched in the vocabulary of NMR. Upfield simply means farther to the right-hand side of the spectrum, and downfield simply means farther to the left-hand side of the spectrum.

4.4.4 Solvents Used in NMR Spectroscopy

A compound, which is free of proton, i.e., which does not give absorption of its own in NMR spectrum, should be used as a solvent. However, the solvent should be capable of dissolving at least 10% of the compound under investigation. The commonly used solvents in NMR spectroscopy are as follows: (i) carbon tetrachloride (CCl_4), (ii) deuterochloroform ($CDCl_3$), (iii) deutero dimethyl sulphoxide (DMSO-d_6), (iv) deuterobenzene (C_6D_6), (v) trifluoroacetic acid, etc.

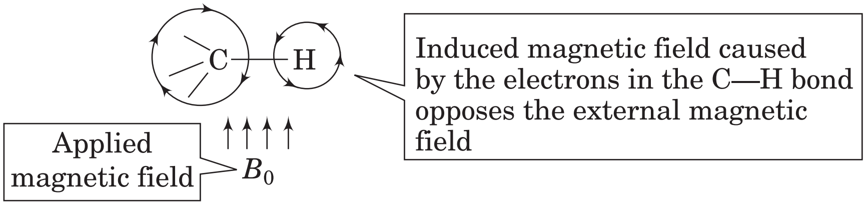
These solvents differ considerably as regards their polarity and because of this, NMR spectrum of a compound measured in one solvent may be slightly different from that measured in another solvent of different polarity. Hence, it is important to mention the solvent used in an NMR spectrum. Hydrogen bonding also changes the value of δ in this technique. Since H-bonding involves electron cloud transfer from hydrogen atom to a neighbouring electronegative atom (O, N, etc.), the H-atom experiences a net deshielding effect. At higher concentrations, strong intermolecular H-bonding occurs in compound containing —OH or —NH_2 group. For this, deshielding of proton is greater and the signal appears at higher δ values than that at low concentrations.

Some important characteristics of solvents used in NMR spectral studies are:

(i) it should be chemically inert and magnetically isotropic,
(ii) it should not contain hydrogen atom, and
(iii) it should dissolve the sample to a reasonable extent.

4.4.5 Chemical Shift

When a molecule is placed in a magnetic field, its electrons are caused to circulate. Circulation of electrons about the proton itself generates an *induced magnetic field* which remain aligned in such a way that it opposes the applied magnetic field. The field felt by the proton is thus diminished, and the proton is said to be **shielded**. For a proton of a C—H bond, this may be shown as follows:



Induced magnetic field caused by the electrons in the C—H bond opposes the external magnetic field

Applied magnetic field

Circulation of electrons—specifically, π electrons—about nearby nuclei generates a field that either opposes or reinforces the applied field at the proton, depending on the proton's location. If the induced field opposes the applied field, the proton is shielded as before. If the induced field reinforces the applied field, the field felt by the proton is augmented, and the proton is said to be deshielded.

Compared with a naked proton, a shielded proton requires a higher applied field strength and a deshielded proton requires a lower applied field strength to provide the particular effective field strength at which absorption occurs. Shielding thus shifts the absorption upfield and deshielding shifts the absorption downfield. Such shifts in the position of NMR absorptions from the signal for the reference compound, arising from shielding and deshielding of protons caused by electrons, are called *chemical shift*. These changes are termed chemical shifts because these shifts result from the circulation of electrons in a chemical bond.

To compare chemical shifts displayed by different kinds of proton, it is necessary to accept a compound whose absorption can be taken as a reference point on a chemical shift scale. It has been observed that the twelve equivalent protons of tetramethylsilane [TMS, $(CH_3)_4Si$] give a single sharp line in a region where generally no other kind of protons absorb, and so, it is the standard reference compound which is universally accepted. It is chosen because it is a volatile liquid, b.p. 26.5°C and is inert to most reagents. Also, it is soluble in most organic liquids. Furthermore, silicon, being more electropositive than carbon tends to donate electron density to the methyl groups, thereby increasing their shielding. The relatively high shielding of protons in TMS causes it to resonate upfield, well clear of most common organic protons commonly encountered in organic compounds. Recently a substitute of TMS, termed as DSS (sodium 2,2-dimethyl-2-silapentane-5-sulphonate, $Me_3SiCH_2CH_2CH_2SO_3Na$) is also in use as internal reference standard in aqueous solution for running NMR spectra of compounds soluble in D_2O.

The orientation of the spectrum on the chart is adjusted electronically so that the TMS peak coincides with the zero grid line. Peak positions are measured in frequency units (hertz) downfield from the TMS peak and this is because $\nu \propto B_0$. However, it is not convenient to express the chemical shift in Hz since it is proportional to the radio frequency of the various spectrometers (e.g., 60 MHz, 100 MHz, etc.) the field must match. When reporting chemical shift in frequency units (Hz), the radio frequency of the instrument must be specified. For instance, a chemical shift of 437 Hz (for $CHCl_3$ proton) with a 60 MHz instrument appears at 2,185 Hz with a 300 MHz instrument. If, however, it is expressed as fraction of the particular radio frequency used, a chemical shift has a constant value that is independent on the radio frequency and the magnetic field at the NMR spectrometer employs. The chemical shift positions are frequently expressed in δ (delta) units which are defined as differences in ppm (parts per million) from the TMS signal, i.e., the zero point on the δ scale. The δ unit is a proportionality and is thus dimensionless. The δ values for equivalent protons are the same on a 60 MHz spectrometer or on a 100 MHz spectrometer, i.e., independent of the radio frequency used. For example, the δ value of $CHCl_3$ proton is 7.28 ppm irrespective of the instrument used.

$$\text{Chemical shift } (\delta) = \frac{\begin{array}{c}\text{Observed chemical shift (Hz) from TMS, i.e.,}\\ \text{(Position of signal – Position of TMS peak)}\end{array}}{\text{Radio frequency of the spectrometer}} \times 10^6$$

Thus, the chemical shift for the proton in chloroform in a 60 or 300 MHz instrument is the same:

$$\delta = \frac{(437\text{ Hz} - 0\text{ Hz})}{60\text{ MHz}} \times 10^6 = \frac{(2{,}185\text{ Hz} - 0\text{ Hz})}{300\text{ MHz}} \times 10^6 = 7.27\text{ ppm}$$

If the radio frequency is used in MHz to calculate the value of δ, the resulting number becomes too small. Because of this, it is multiplied by 10^6 so that we obtain a value which can be conveniently handled.

If a signal is shifted towards the left on the chart paper (larger chemical shift), we say that it is shifted **downfield**. A downfield shift actually corresponds to decreased shielding around a nucleus, i.e., deshielding. If a signal is shifted towards the right (smaller chemical shift), we say that it is shifted **upfield**. An upfield shift corresponds to increased shielding around a nucleus.

Another standard scale is the τ (tau) scale. This is also independent of the frequency and defines the TMS peak as occurring at 10τ. To convert from δ to τ, the chemical shift as measured on the δ scale is subtracted from 10, i.e., $\tau = 10 - \delta$. The relationship between these two scales, position of TMS signal and the correlation of shielding effects with the magnetic field are shown in Figure 4.15.

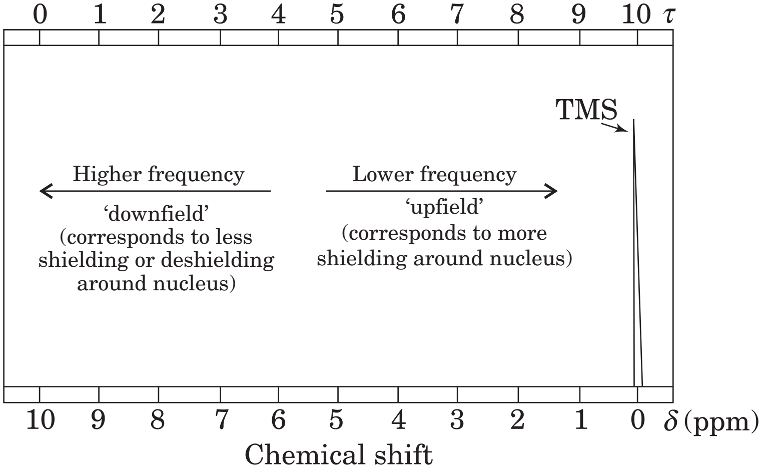

0 1 2 3 4 5 6 7 8 9 10 τ
TMS
Higher frequency
'downfield'
(corresponds to less shielding or deshielding around nucleus)
Lower frequency
'upfield'
(corresponds to more shielding around nucleus)
10 9 8 7 6 5 4 3 2 1 0 δ (ppm)
Chemical shift

Figure 4.15 Scales of NMR spectra

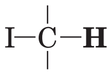
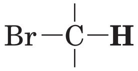
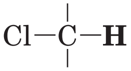
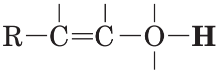
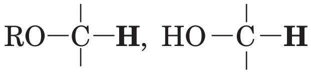
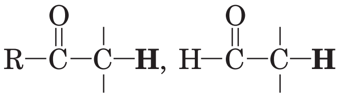
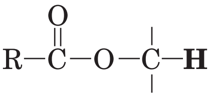
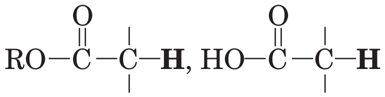
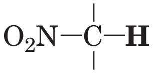
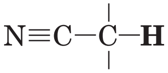
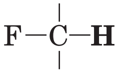
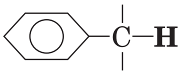
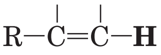
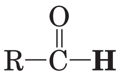
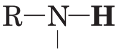
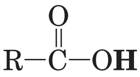
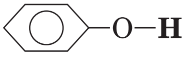
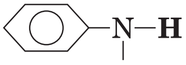
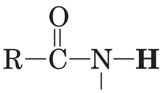
The following diagram will help to keep track of the terms associated with proton NMR spectroscopy:

Protons in electron-poor environments	Protons in electron-dense environments
deshielded protons downfield high frequency large δ values	shielded protons upfield low frequency small δ values
← δ ppm ← frequency (ν)	

4.4.6 Factors Influencing Chemical Shift

The chemical shifts of different types of protons are influenced by local environments. The value of chemical shifts of different types of protons, listed in Table 4.10 are illustrative.

Table 4.10 Approximate chemical shift ranges (ppm) for selected types of protons

$R{-}C\mathbf{H}_3$	0.7–1.3	 $I{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H}$	2.0–4.0
$R{-}C\mathbf{H}_2{-}R$	1.2–1.4	 $Br{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H}$	2.7–4.1
$R_3C\mathbf{H}$	1.4–1.7	 $Cl{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H}$	3.1–4.1
 $R{-}\overset{|}{C}{=}\overset{|}{C}{-}\overset{|}{\underset{|}{O}}{-}\mathbf{H}$	1.6–2.6	 $RO{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H},\ HO{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H}$	3.2–3.8
 $R{-}\overset{O}{\overset{\|}{C}}{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H},\ H{-}\overset{O}{\overset{\|}{C}}{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H}$	2.1–2.4	 $R{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H}$	3.5–4.8
 $RO{-}\overset{O}{\overset{\|}{C}}{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H},\ HO{-}\overset{O}{\overset{\|}{C}}{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H}$	2.1–2.5	 $O_2N{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H}$	4.1–4.3
 $N{\equiv}C{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H}$	2.1–3.0	 $F{-}\overset{|}{\underset{|}{C}}{-}\mathbf{H}$	4.2–4.8
	2.3–2.7	 $R{-}\overset{|}{C}{=}\overset{|}{C}{-}\mathbf{H}$	4.5–6.5
$R{-}C{\equiv}C{-}\mathbf{H}$	1.7–2.7	$Ar{-}\mathbf{H}$	6.5–8.0
$R{-}S{-}\mathbf{H}$	1.0–4.0[a]	 $R{-}\overset{O}{\overset{\|}{C}}{-}\mathbf{H}$	9.0–10.0
 $R{-}\underset{|}{N}{-}\mathbf{H}$	0.5–4.0[a]	 $R{-}\overset{O}{\overset{\|}{C}}{-}O\mathbf{H}$	11.0–12.0
$R{-}O{-}\mathbf{H}$	0.5–5.0[a]		
	4.0–7.0[a]		
	3.0–5.0[a]		
 $R{-}\overset{O}{\overset{\|}{C}}{-}\underset{|}{N}{-}\mathbf{H}$	5.0–9.0[a]		

[a] The chemical shift of these groups are variable, depending not only on the chemical environment in the molecule but also on solvent, concentration and temperature

We shall now discuss some important factors influencing the chemical shifts. These factors are as follows:

(a) *Electronegativity of nearby atoms or group (inductive effect)*
(b) *State of hybridization of adjacent atoms*
(c) *Resonance effect*
(d) *Hydrogen bonding*
(e) *Steric effect (van der Waals deshielding)*
(f) *Diamagnetic effects of π-bonds (magnetic anisotropy)*

(a) Electronegativity of nearby atoms or groups (inductive effect): Protons in different environments experience different degrees of shielding and have different chemical shifts. Protons on saturated carbon atoms not attached to hetero atoms (N, O, halogen) absorb far to the right in the spectrum. This higher field absorption is due to the shielding caused by the surrounding C—C and C—H bonding electrons. For example, the three protons of a CH_3-group (which give only one absorption signal due to the same electronic environment), when attached to another carbon with no nearby substituent, appear at about δ 0.7–1.3. However, when the electron density is reduced due to the inductive effect of a neighbouring electronegative atom, the shielding effect due to electrons is reduced with the result that resonance can now occur at a lower value of the applied field (deshielding). It is, therefore, understandable that protons of a methyl group attached to an electronegative atom resonate, i.e., appear at lower field than those of a methyl group attached to carbon. Thus, it can be said that shielding and deshielding of protons depend upon the inductive effect of the neighbouring atom or group. The electron-withdrawing group reduces electron density around the proton and results in its deshielding, while the electron-releasing group (mostly alkyl) increases the electron density around the proton and results in its shielding.

Examples

1. Since the electronegativity of halogen increases from I to F (F = 4, Cl = 3.1, Br = 2.8, I = 2.5), the chemical shift for protons of halomethane increases in the following order:

CH_3—I	CH_3—Br	CH_3—Cl	CH_3—F
δ 2.16	δ 2.68	δ 3.05	δ 4.26

2. The influence of electronegativity of atoms may also be observed in the following series (where the electronegativity order is F > O > N > C):

CH_3—F	CH_3—OCH_3	$(CH_3)_3N$	CH_3CH_3
δ 4.26	δ 3.30	δ 2.30	δ 0.9

3. The deshielding effects of electronegative groups are cumulative as illustrated by the following sequence:

CH_3—Cl	CH_2Cl_2	$CHCl_3$
δ 3.05	δ 5.30	δ 7.27

4. The deshielding effect of halogens diminishes with increase in distance.

—$C\mathbf{H}_2$—Br	—$C\mathbf{H}_2$—CH_2Br	—$C\mathbf{H}_2$—CH_2CH_2Br
δ 3.30	δ 1.69	δ 1.25

5. Carbon is more electronegative than hydrogen. Because of this, every replacement of hydrogen by an alkyl group causes a downfield shift in the resonance of any

remaining hydrogen on it. Thus, methyl, methylene, methine, hydrogens come into resonance at successively lower fields.

$MeC\mathbf{H}_3$	$Me_2C\mathbf{H}_2$	$Me_3C\mathbf{H}$
$\delta\,0.86$	$\delta\,1.33$	$\delta\,1.68$

6. Replacement of hydrogens of methane by phenyl group also causes downfield shift (deshielding).

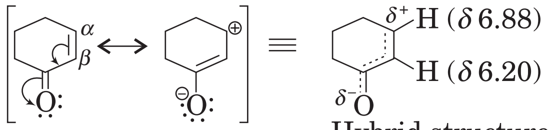
$C\mathbf{H}_4$	$PhC\mathbf{H}_3$	$Ph_2C\mathbf{H}_2$	$Ph_3C\mathbf{H}$
$\delta\,0.23$	$\delta\,2.34$	$\delta\,3.92$	$\delta\,5.63$

7. Due to extensive deshielding (depletion of electron density), the methine hydrogen in diphenylmethyl cation appears at a much downfield.

$$Ph_2\overset{\oplus}{C}\mathbf{H}$$
$$\delta\,9.30$$

(b) State of hybridization of adjacent atoms: Hydrogens attached to an *sp*^{3}-hybridized carbon typically have signals at $\delta\,0.8$ to 1.7. Vinylic hydrogens $\gt C{=}C\lt_{\mathbf{H}}$ are considerably deshielded and their signals appear at $\delta\,4.6$ to 5.7. This is due to the fact that a vinylic hydrogen is attached to an *sp*^{2}-hybridized carbon which is more electronegative than an *sp*^{3}-hybridized carbon. However, signals for acetylenic hydrogens attached to more electronegative C_{sp} carbon appear anomalously at $\delta\,2.0$ to 3.0 (i.e., between C_{sp3}—H and C_{sp2}—H). If the chemical shift of vinylic hydrogens ($\delta\,4.6$—5.7) were caused entirely by the hybridization state of carbon, then the chemical shift of acetylenic hydrogen should be even greater than that of vinylic hydrogens. Yet the chemical shift of acetylenic hydrogens ($—C\equiv C—\mathbf{H}$) is only $\delta 2.0$ to 3.0. That the chemical shift of acetylenic hydrogens is abnormally small or the chemical shift of vinylic hydrogen is abnormally large is due to the fact that not only electronegativity but also some other factor must be contributing to the magnitude of chemical shift. This factor is called **magnetic anisotropy** (magnetic induction from π bonds).

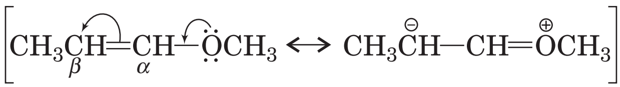
(c) Resonance effect: Resonance or mesomeric effect plays an important role towards the variation in electron density in protons which is reflected in the positions of their signals in the NMR spectra. For example, in cyclohexenone, the carbonyl group withdraws electrons from the β-position by resonance so as to deshield this position and consequently, the proton at this position shows a peak at a distinctly downfield position ($\delta 6.88$) compared to cyclohexane ($\delta\,5.57$).



Resonance in 2-cyclohexenone

Hybrid structure

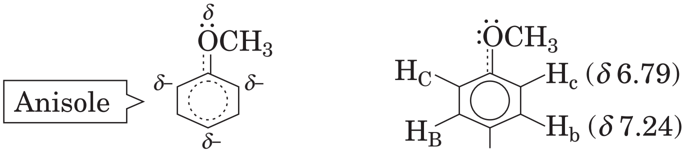
Similarly, in the following substituted vinyl ether, the oxygen atom deshields the α proton by –I effect and shields the β-proton by +R effect; α-proton signal appears at δ = 6.2, whereas β-proton signal appears at δ = 4.6.



$$\left[CH_3\underset{\beta}{C}H=\underset{\alpha}{C}H-\ddot{O}CH_3 \leftrightarrow CH_3\overset{\ominus}{C}H-CH=\overset{\oplus}{O}CH_3\right]$$

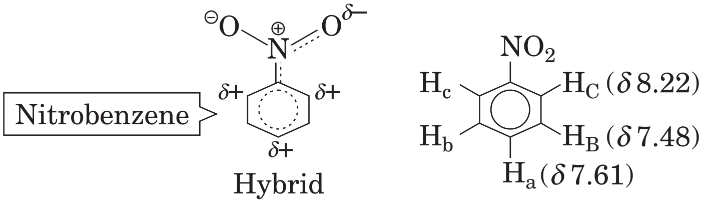
Resonance in 1-methoxyprop-1-ene

The chemical shifts of protons *ortho*, *meta* and *para* to a substituent on an aromatic ring are correlated with electron densities caused by that substituent at that particular position. For example, the *ortho*- and *para*-protons of anisole are shielded, since the —OMe group donates electrons to the *ortho*- and *para*-positions by resonance effect (+R) and as a consequence, the *ortho*- and *para*-protons show signals upfield than benzene (δ 7.27).



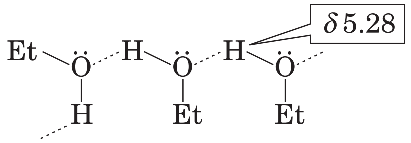
Hybrid structure

In nitrobenzene, the —NO_2 group withdraws electrons by its –R and –I effects from *ortho*- and *para*-positions more than the *meta*-position (by only its –I effect). So, the *ortho*- and *para*-positions will be more deshielded, i.e., will show signals downfield than benzene. The *meta*-position will also show slight downfield signal than benzene (δ 7.27).

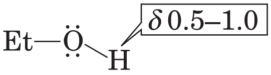


Hybrid structure

(d) Hydrogen bonding: Hydrogen bonding involves transfer of electron cloud from the H atom to the attached electronegative atom (O, N, etc.). This electron withdrawal from a proton depletes the electron density around it and as a consequence, downfield shift occurs. The greater the degree of H-bonding, the greater the downfield shift (higher δ value) of its resonance. The position of resonance of OH and NH protons of alcohols and amines is unpredictable because the extent of H-bonding depends on concentration, solvent and temperature. For example, in spectrum of neat ethanol (in which its molecules remain highly associated through intermolecular H-bonding), the OH proton appears as a slightly broadened peak at δ 5.28 ppm. However, at a concentration of about 5–20% in a non-polar solvent like CCl_4, when the association breaks up (into trimers or dimers), the OH proton resonates upfield in between δ 2.0–4.0 and at infinite dilution, when there is practically no hydrogen bonding, proton resonance occurs near δ 0.5–1.0. The extent of intermolecular H-bonding decreases with rise in temperature. Because of this, the OH proton resonates upfield at an increased temperature.

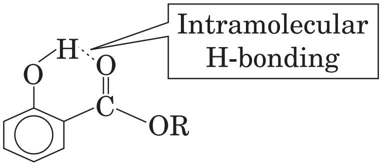


Hydrogen bonded ethanol
(neat liquid or much concentrated solution)



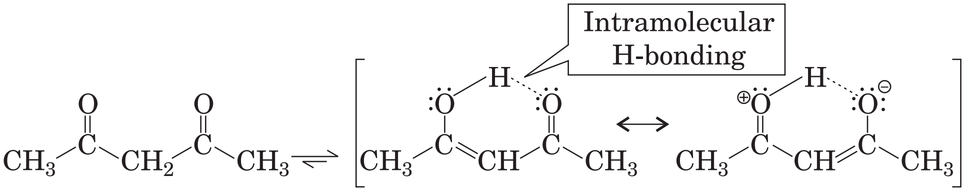
Relatively free ethanol
(dilute solution)

Intramolecular H-bonding, however, remains practically unaffected on dilution and ^1H NMR spectrum from such systems remains virtually unchanged by changing the concentration. For example, in salicylates, no change in chemical shift occurs on dilution.



Salicylates
(δ_{OH} = 10–12; no change on dilution)

In the enol form of a *β*-diketone, say, acetyl acetone, there occurs intramolecular hydrogen bonding which is further strengthened by resonance. This causes a great deshielding effect and in fact, the OH proton absorbs at the negative tau value (–4.9*τ*, i.e., *δ* 14.9). The position of the peak does not vary with change in concentration in the solvent $CDCl_3$. But, increase in temperature makes the hydrogen bonds weaker so that the peak is observed to shift to lower *δ*.



Keto-form *Enol*-form

Acetyl acetone

(e) Steric effect (van der Waals deshielding): In overcrowded molecules, it is possible that some proton may be occupying sterically hindered position. Clearly, the electron cloud of a bulky group (the hindering group) will tend to repel the electron cloud surrendering the proton. Therefore, such a proton will be deshielded and will resonate at slightly higher value of *δ* than expected in the absence of this effect.

(f) Diamagnetic effects of *π*-bonds (magnetic anisotropy): In addition to the through-bond inductive effects, the applied magnetic field induces unsymmetric magnetic fields about *π*-bond and this is because *π*-electrons are more polarizable than *σ*-electrons and free to move in a circular path in response to a magnetic field. The effect of these induced fields which operates through space may be large or small. The induced field opposes the applied field in some region and reinforces the latter in some other region of the molecule. Thus, the protons lying in the former region are shielded while those lying in the latter region are deshielded. Such shielding and deshielding effects on the proton due to induced magnetic field are called *anisotropic effects*. Since the nature of the induced field around the π-bond is not similar, i.e., not isotropic, it is called anisotropic effect.

The deshielding effect of protons attached to C═C is higher than that can be accounted for by the inductive effect of C_{sp2} alone. Aldehyde and aromatic protons are much more deshielded. Acetylenic protons appear at relatively low value of δ. The value of δ in each case can be justified by explaining the manner in which the π electrons circulate under the influence of the applied magnetic field. Let us consider an alkene, e.g., ethylene ($CH_2{=}CH_2$). It is so oriented that the plane of the molecule is at right angles to the applied field. Induced circulation of π electrons generates an induced magnetic field which is diamagnetic around carbon atoms and paramagnetic in the region of the protons. A small field is, therefore, required for resonance resulting in their deshielding. The highly deshielded position of aldehydic proton is attributed to a combination of a strong inductive effect and the paramagnetic deshielding effect caused by the carbonyl π-electrons. These are shown in Figure 4.16.

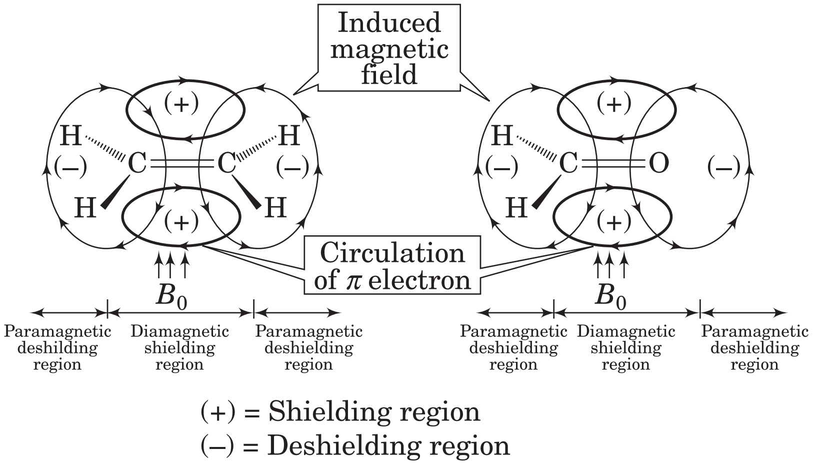

Induced magnetic field
(+)
H
C
C
H
(–)
(–)
H
H
(+)
H
C
O
(–)
(–)
H
(+)
(+)
Circulation of π electron
B0
B0
Paramagnetic deshilding region
Diamagnetic shielding region
Paramagnetic deshielding region
Paramagnetic deshielding region
Diamagnetic shielding region
Paramagnetic deshielding region
(+) = Shielding region
(–) = Deshielding region

Figure 4.16 Paramagnetic deshielding effect experienced by the protons of ethylene and formaldehyde

The NMR spectrum of benzene consists of a sharp, single line at δ 7.27. This peak is due to six equivalent ring protons. The value of chemical shift is, however, somewhat surprising. The signal appears farther downfield than is normally observed for the hydrogens attached to the double bonds of alkenes (δ 4.5–6.5). This unusual chemical shift of the protons of benzene may be well explained by anisotropic effects. When the π-electron system of an aromatic compound is subjected to an applied magnetic field, B_0, the π-electrons are made to 'flow' in a circle around the ring. The flow is called a **ring current**.

This ring current generates an induced magnetic field that adds to B_0 in the region near the benzene protons. The net result is that the benzene protons are deshielded and a lower applied field is required to bring them into resonance (downfield: high δ value). The induced magnetic field opposes the applied field B_0 in the centre of the benzene ring. The magnetic anisotropy in benzene is shown in Figure 4.17. It is to be noted that the shift of benzylic protons is less than the shift of benzene protons because benzylic protons are further from the ring.

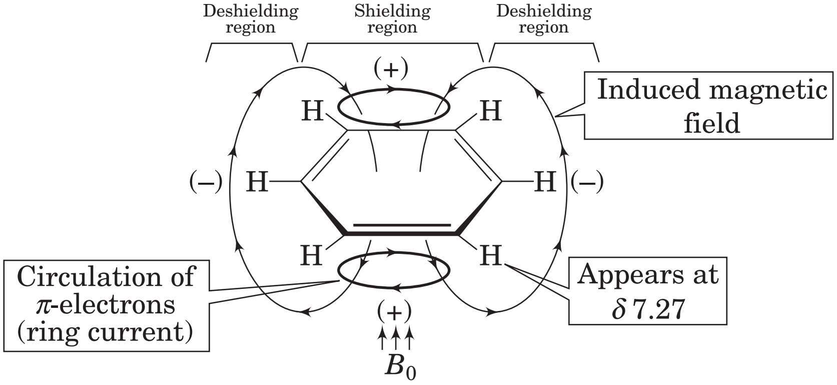


Figure 4.17 **Paramagnetic deshielding effect experienced by benzene protons**

[It appears that only an aromatic molecule can produce a ring current of this magnitude and direction. Therefore, the presence of a ring current, indicated by unusual chemical shifts, is the most common experimental criterion of *aromaticity*.]

Unlike ethylinic and aldehydic protons, the acetylenic protons appear at high field (low δ values). Circulation of electrons around the triple bond occurs in a way so that the proton of an alkyne (e.g., acetylene) experiences a diamagnetic shielding effect. The acetylene molecule is linear. When the axis of acetylene molecule lies parallel to the direction of the applied field B_0, the cylindrical sheath of π-electrons is induced to circulate around the axis. This electronic motion induces a magnetic field which, at the acetylenic protons, opposes the applied field B_0. The net result is that the acetylenic protons are shielded and a higher applied field is required to bring them into resonance (upfield: low δ-value). This is shown in Figure 4.18.

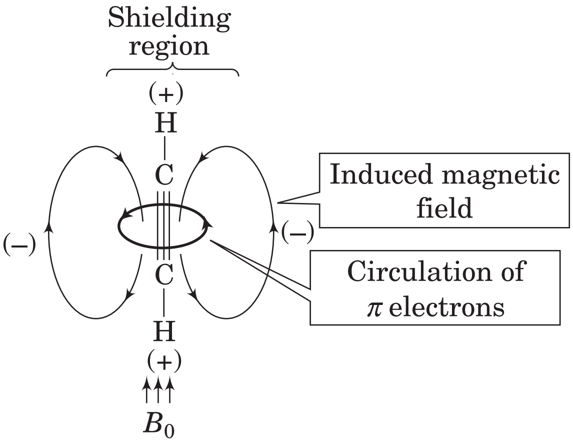


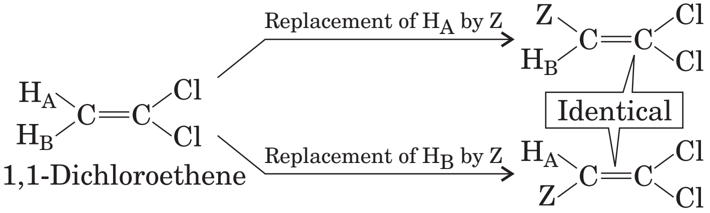
Figure 4.18 **Shielding of acetylenic protons in parallel orientation to the applied field**

In fact, the diamagnetic shielding of acetylenic protons is a result of two factors. When the molecule is aligned perpendicular to the magnetic field B_0, the acetylenic protons are deshielded, just as in the case of ethylenic protons. But this deshielding component is smaller than the shielding component, because the electrons are not as free to move in this direction. When averaged over all possible orientations, the effect is a net diamagnetic shielding.

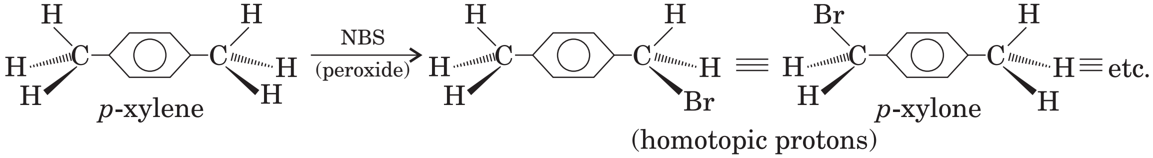
4.4.7 Chemical Shift and Stereochemistry

Two or more protons that are in identical environments have the same chemical shift and are, therefore, give only one proton NMR signal. For most compounds, protons that are in the identical environment are also equivalent in chemical reactions. It, thus, follows that chemically equivalent protons have the same chemical shift and they are said to be *chemical shift equivalent* or *isochronous*.

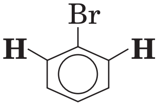
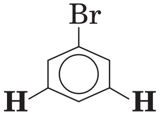
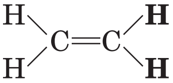
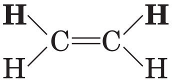
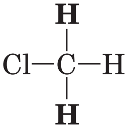
In general, hydrogens having the same chemical shift are either (a) equivalent (homotopic) or (b) enantiotopic. This can be demonstrated by replacing each hydrogen in turn with some other group, say, Z. If in making these substitutions we get the same compound from each replacement, then the protons are chemically equivalent and are chemical shift equivalent. For example, the protons H_A and H_B in 1,1-dichloroethene are equivalent (homotopic) because replacement of H_A and H_B by a group Z gives the same product. This means that H_A and H_B must be chemical shift equivalent or isochronous.



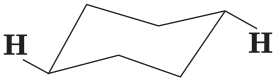
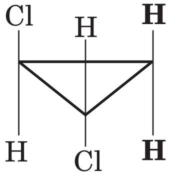
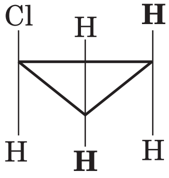
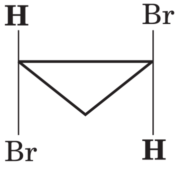
For the methyl hydrogens of *p*-xylene, we can think an actual chemical reaction, e.g., benzylic bromination, that demonstrates their equivalence. This reaction produces the same monobromo derivative regardless of which of the six hydrogen atoms is replaced. Therefore, these protons are chemically equivalent and are chemical shift equivalent.

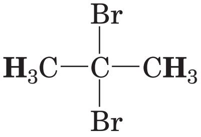


Other examples of equivalent (homotopic) protons include those shown in bold face (**H**) in the following structures:

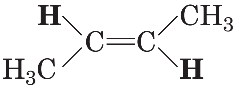
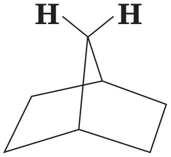






$\mathrm{Cl{-}\overset{\mathbf{H}}{\underset{\mathbf{H}}{C}}{-}H}$

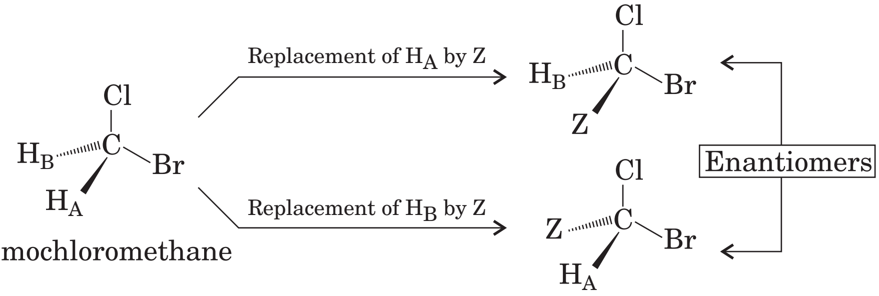







$\mathrm{\mathbf{H_3}C{-}\overset{Br}{\underset{Br}{C}}{-}C\mathbf{H_3}}$

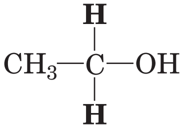



Enantiotopic hydrogens can be identified by using the same type of substitution process. However, in this case replacing the two protons in turn with a group Z will form two enantiomers. For example, protons H_A and H_B in bromochloromethane are enantiotopic. replacement of the first one, and then the other, with a group Z leads to two enantiomers. This means that H_A and H_B are chemical shift equivalent or isochronous.

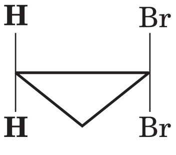
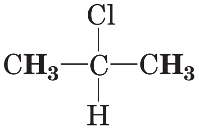


Bromochloromethane

Other examples of enantiotopic hydrogens include those shown in bold face (**H**) in the structures below:



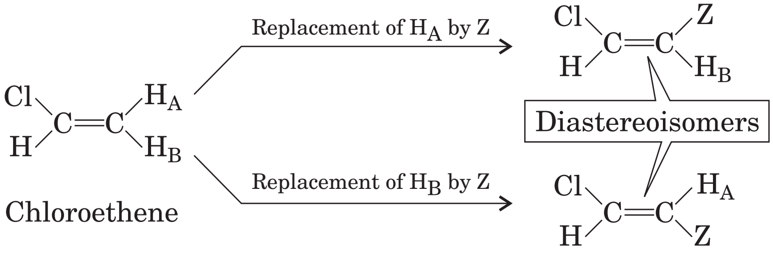
$\mathrm{CH_3{-}\overset{\mathbf{H}}{\underset{\mathbf{H}}{C}}{-}OH}$

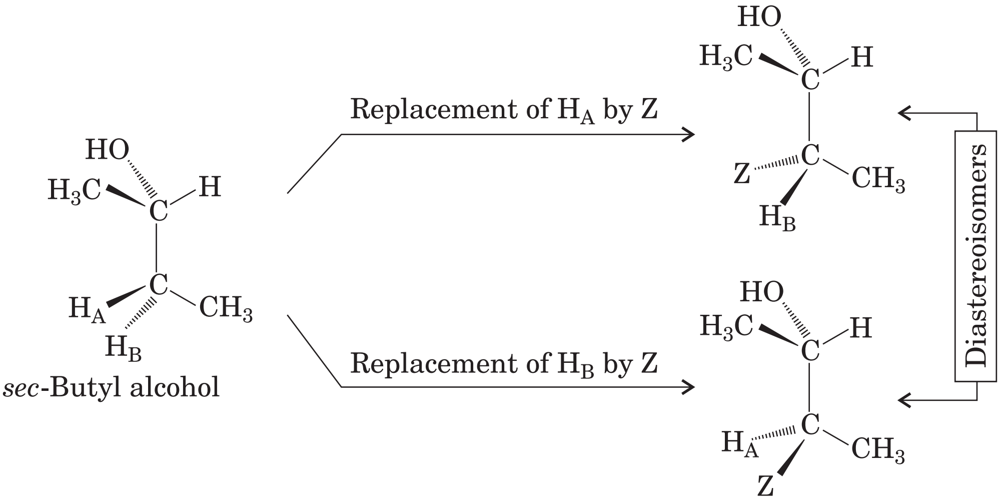
$\mathrm{C\mathbf{H_3}{-}\overset{Cl}{\underset{H}{C}}{-}C\mathbf{H_3}}$

Each set of chemically equivalent protons in a compound produces a separate signal in its ^{1}HNMR spectrum. Thus, 1-chloropropane ($CH_3CH_2CH_2Cl$) has three signals in its ^{1}HNMR spectrum because it has three sets of chemically equivalent protons. Similarly, 2-bromopropane ($CH_3CHBrCH_3$) has two sets of chemically equivalent protons, so it has two signals in its ^{1}HNMR spectrum. (It is to be noted that sometimes the signals are not sufficiently separated and overlap each other. When this happens, one sees less number of signals than expected.)

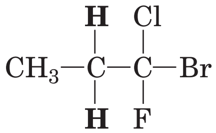
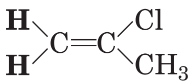
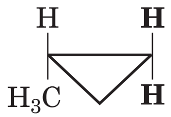
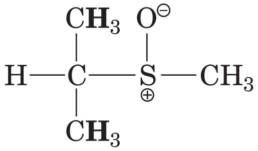
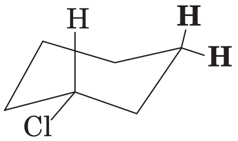
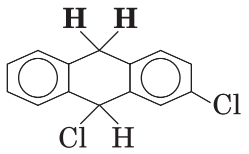
Protons that are diastereotopic will have different chemical shifts. Diastereotopic protons can be recognized by using the substitution criterion. If replacement of each hydrogen atom by a group, *Z*, gives compounds that are diastereomers, the two hydrogens are said to be diastereotopic. Diastereotopic protons do not have the same chemical shift, i.e., they give rise to different proton NMR signals. Therefore, diastereotopic protons are said to be *chemical shift nonequivalent* or *anisochronous*. For example, the two protons of the $=CH_2$ group of chloroethene are diastereotopic.



The two methylene ($—CH_2—$) protons of *sec*-butyl alcohol are also diastereotopic because similar replacement produces two diastereoisomers.



So, the H_A and H_B protons in both the cases are chemical shift nonequivalent. In the following examples, the protons in bold face are diastereotopic and therefore, anisochronous.

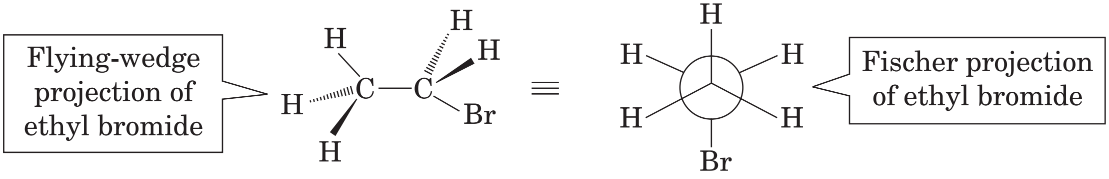
Enantiotropic hydrogens may not have the same chemical shift if the compound is dissolved in an optically active solvent. However, most proton nmr spectra are determined using optically inactive solvents and in this situation enantiotropic protons have the same chemical shift. The chemical shift of diastereotopic hydrogens does not depend upon the solvent in which the spectrum is taken.

4.4.8 NMR and Rate Processes (Equivalence of Protons: a Closer Look)

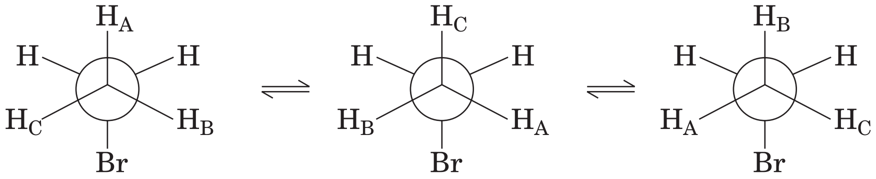
Equivalence or nonequivalence of protons is fundamental to the NMR spectrum, since it affects both the number of signals and their splitting. Let us look more closely at equivalence, and see how it is affected by the rate at which certain molecular changes, for example, rotation about the carbon—carbon single bonds, occur.

Professor John D. Roberts (of California Institute of Technology), a pioneer in the application of NMR spectroscopy to problems of organic chemistry, has compared the NMR spectrometer to a camera with a relatively low shutter speed. Such a camera is able to photograph the spokes of a wheel in different ways depending upon the speed with which the wheel spins: as sharp, individual spokes when it spins slowly; as blurred spokes when the spinning is faster; and as a single circular smear when the spinning is much faster. Similarly, if the molecular change is fast, the NMR spectrometer sees a proton in its average environment and gives a smeared-out picture. But, if the molecular process is slow, the spectrometer sees the proton in each of its environments.

Let us examine the effects on the NMR spectrum of rotations about single bonds and for this, let us consider the spectrum of ethyl bromide (CH_3CH_2Br). The most stable conformation of ethyl bromide is the one in which the groups are perfectly staggered. In this staggered conformation, one hydrogen of the methyl group is *anti* to bromine and two hydrogens are *gauche*. The anti proton is, therefore, in a different environment from the others, and is not equivalent to them at that moment. If NMR spectrometer were to detect this particular conformation of ethyl bromide, it would show the *anti* hydrogen of the CH_3— group at a different chemical shift.


Flying-wedge projection of ethyl bromide
H
H
H
H
H
C
C
Br
≡
H
H
H
H
H
Br
Fischer projection of ethyl bromide

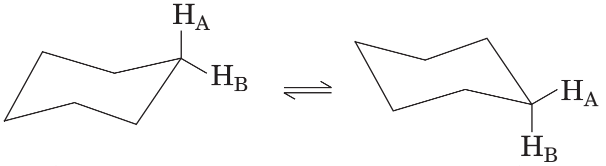
However, it is known that in the spectrum of ethyl bromide, the three methyl protons give a single signal (a signal that is split into a triplet by spin–spin coupling with the two protons of the adjacent carbon) and this is because at room temperature the groups connected by carbon–carbon single bond rotate approximately 1 million times per second. The 'shutter speed' of the spectrometer is too slow to 'photograph' this rapid rotation; instead, it photographs the methyl protons in their average environments (one-third *anti* and two-third *gauche*), and in this sense, it gives us a blurred picture of the methyl group.



(In one of these conformations a given proton, say H_A,
is *anti* to Br and in other two it is *gauche.*)

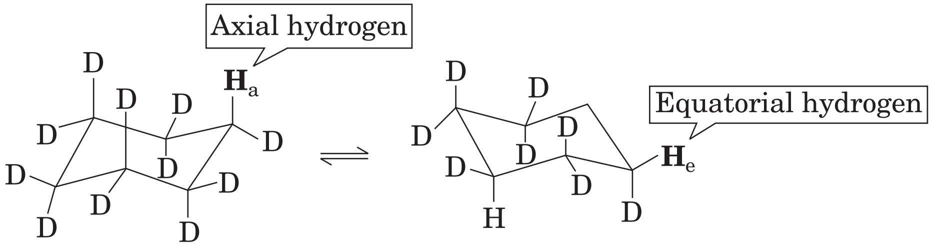
Rotations about single bonds slow down as the temperature of the compound is lowered. When we determine the spectrum at a sufficiently low temperature, this slowing of rotations allows us to 'see' the different conformations of a molecule.

An example of this phenomenon, and one that also shows the usefulness of deuterium labelling, can be seen in the low temperature proton NMR spectra of cyclohexane and of undecadeuteriocyclohexane ($C_6D_{11}H$). A room temperature, ordinary cyclohexane gives only one signal because interconversion between two chair forms occurs very rapidly and the average environments of six axial and six equatorial protons are identical: half equatorial, half axial. At –70°C, the signal splits into two peaks and at –100°C two clearly separated peaks are obtained. One peak is due to axial protons and the other is due to equatorial protons. In fact, at a much low temperature interconversions are slow and it becomes possible for the NMR spectrometer to 'photograph', i.e., to detect the individual conformation.



(Chair conformations of cyclohexane)

At –100°C, however, undecadeuterocyclohexane gives only two sharp signals of equal intensity. These signals correspond to the axial and equatorial hydrogen atoms of the following two chair conformations.



Undecadeuterocyclohexane

Another example of rapidly occurring process can be seen in the NMR spectrum of ethanol. The NMR spectrum of ordinary ethanol shows the hydroxyl proton as a singlet and the protons of the —CH_2-group as a quartet. In ordinary ethanol, we observe no signal splitting arising from coupling between the —OH and —CH_2-protons even though they are on adjacent atoms. If the NMR spectrum of very pure ethanol is examined, we find that the signal from the hydroxyl proton is split into a triplet, and that the signal from the protons of the —CH_2— group is split into a multiplet of eight peaks. This observation suggests that in very pure ethanol, the spin of the proton of the —OH group couples with the spin of the protons of the —CH_2— group. Whether or not coupling occurs between the hydroxyl proton and the methylene proton depends on the length of time the proton spends on a particular molecule. Protons attached to electronegative atoms with lone pairs such as oxygen can undergo rapid **chemical exchange**, i.e., they can be transferred rapidly from one molecule to another. The chemical exchange in very pure ethanol is relatively slow and as a consequence, the signal splitting of and by the hydroxyl proton is seen in the spectrum. In ordinary (commercial) ethanol, acidic and basic impurities catalyze the chemical exchange; the exchange takes place so rapidly that the hydroxyl proton gives an unsplit signal and those of the methylene protons are split only by coupling with the protons of the —CH_3 group. Therefore, it can be said that rapid exchange causes **spin decoupling**.

The chemical exchange of alcohols catalyzed by the presence of traces of hydrogen chloride in solvents take CCl_4, $CDCl_3$, etc. may be shown as follows:

$$\text{R—O—H} + \text{R—O—H}^* \xrightleftharpoons{10^{-5}\text{s}} \text{R—O—H}^* + \text{R—O—H}$$

(The exchange is much faster than NMR time scale of 10^{-2} to 10^{-3} s)

4.4.9 Peak Area and Proton Counting

A careful inspection of the NMR spectrum of a compound, e.g., toluene, makes it clear that all the signals in a spectrum are not of equal intensity. In fact, the area under each signal (or peak size) is directly proportional to the number of equivalent protons giving rise to the signal. Although a visual comparison of absorption areas gives us rough idea, for an accurate analysis, these peaks are integrated by an *automatic electronic integrating device*. Such an integration appears in the NMR spectrum in the form of *stepped up curves* whose heights are proportional to the areas under the peaks. A look at the spectrum of toluene (Figure 4.19) reveals that the height of integral line for the deshielded protons corresponds to 44.3 divisions, and the one for the shielded protons corresponds to 26.1 divisions. Dividing each by 26.1, we get

$$\frac{44.3}{26.1} = 1.7; \quad \frac{26.1}{26.1} = 1$$

Thus the simplest ratio of the protons is 1.7:1.

Multiplying each number by 3 we get the simplest whole number ratio 5 : 3. We can then conclude that five protons are responsible for the signal at δ 7.17 (C_6H_5—) and three are responsible for the signal at δ 2.34 (—CH_3).

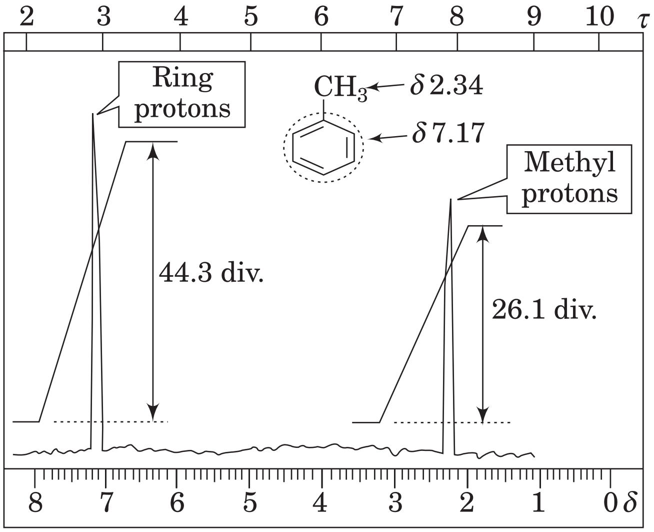


Figure 4.19 NMR spectrum of toluene

4.4.10 Signal Splitting (Spin–Spin Coupling)

Signal splitting is caused by the magnetic fields of protons on nearby atoms. The following spectrum of 1,1,2-tribromoethane shows the signal splitting of different protons (Figure 4.20).

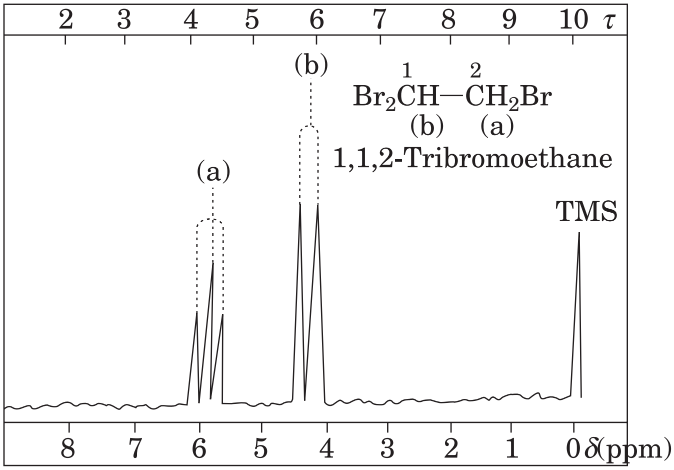
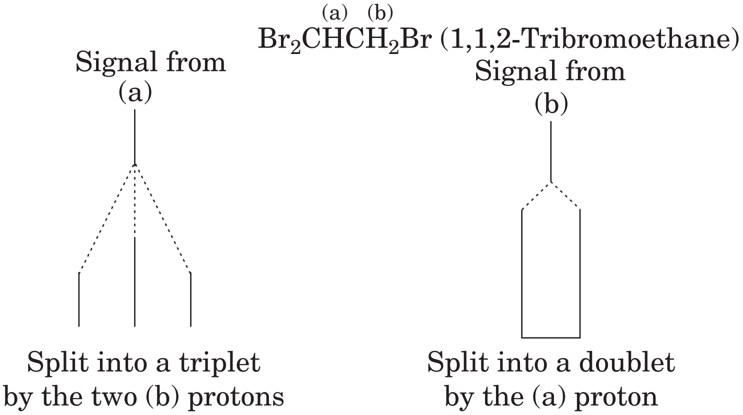
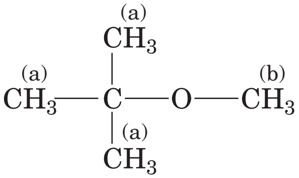


Figure 4.20 NMR spectrum of 1,1,2-tribromoethane

The signal from the two equivalent protons of the —CH_2Br group of 1,1,2-tribromoethane is split into two peaks by the single proton of the —$CHBr_2$ group. The signal from the proton of the $CHCl_2$— group is split into three peaks by the two protons of the —CH_2Cl group. This may further be illustrated as follows:


(a) (b)
Br₂CHCH₂Br (1,1,2-Tribromoethane)
Signal from (a)
Signal from (b)
Split into a triplet by the two (b) protons
Split into a doublet by the (a) proton

Signal splitting arises from a phenomenon known as *spin-spin coupling*. Spin-spin coupling effects are transferred primarily through the bonding electrons and are not usually observed if the protons are separated by more than three σ bonds. Thus, we observe signal splitting from the protons of adjacent σ-bonded atoms in 1,1,2-tribromoethane. However, we could not observe splitting of either signal of *tert*-butyl methyl ether because the protons labelled (b) are separated from those labelled (a) by more than three σ-bonds. Both signals from *tert*-butyl methyl ether would be singlets.

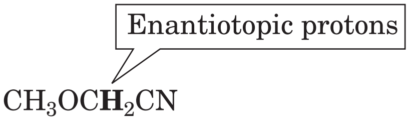


tert-Butyl methyl ether
(no signal splitting)

Signal splitting is not observed for protons that are chemically equivalent (homotopic or enantiotopic). That is, signal splitting does not take place between protons that have exactly the same chemical shift. Thus, we would not expect, and do not find, signal splitting in the signal from the six equivalent hydrogen atoms of ethane. Also, we do not find signal splitting in the signal of enantiotopic protons of methoxy acetonitrile.

$CH_3—CH_3$

Ethane
(no signal splitting)



$CH_3OC\mathbf{H}_2CN$

Methoxy acetonitrile
(no signal splitting)

Let us now explain how signal splitting arises from coupled sets of protons that are not chemical shift equivalent.

We know that the protons can be aligned in only two ways in an external magnetic field: with the field or against it. Therefore, the magnetic moment of a proton on an adjacent atom (C, O, N) may affect the magnetic field at the proton whose signal we are observing in two ways. The occurrence of these two slightly different effects causes the appearance of a peak somewhat upfield (from where the signal might have occurred) and another peak somewhat downfield.

Figure 4.21 shows how the two possible orientations of a neighbouring proton H_b splits the signal from the proton H_a (the two protons are not equivalent).

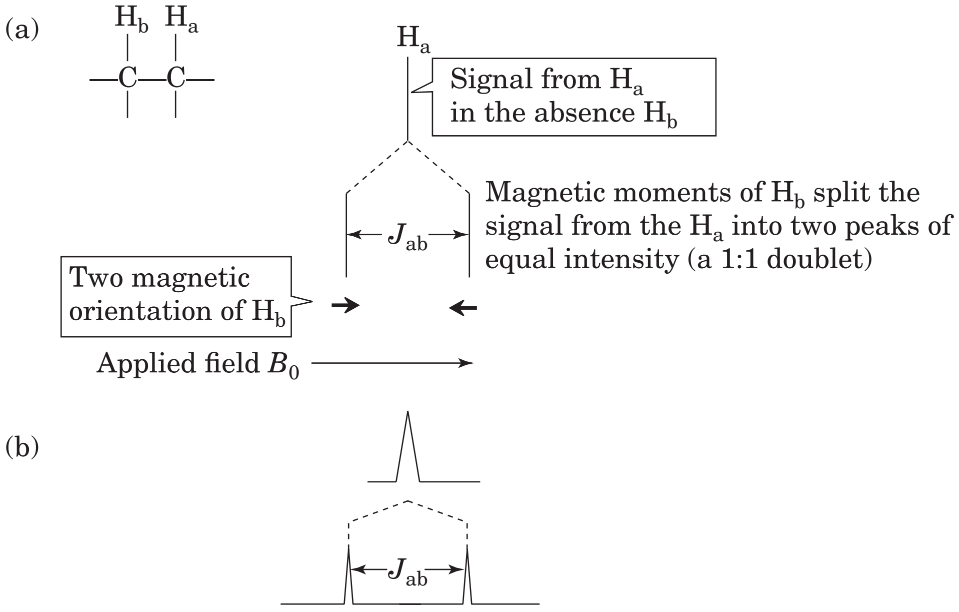

(a)
H_b H_a
—C—C—
H_a
Signal from H_a in the absence H_b
Magnetic moments of H_b split the signal from the H_a into two peaks of equal intensity (a 1:1 doublet)
J_{ab}
Two magnetic orientation of H_b
Applied field B_0
(b)
J_{ab}

Figure 4.21 **Signal splitting arising from spin-spin coupling. A theoretical analysis is shown in (a) and the actual appearance of the spectrum in (b). The distance between the centres of the peaks of the doublet is called the coupling constant, J_{ab}**

The two equivalent protons on an adjacent carbon (or carbon atoms) split the signal from an absorbing proton in a 1:2:1 triplet. Figure 4.22 illustrates how this pattern occurs.

In compounds of either type (A or B), both protons may be aligned with the applied field. This orientation causes a peak to appear at a lower applied field strength than would occur in the absence of the two H_b atoms. Conversely, both protons may be aligned against the applied field. This orientation of H_b protons causes a peak to appear at higher applied field strength than would occur in their absence. Finally, there are two ways in which the two protons may be aligned in which one opposes the applied field and one reinforces it. These arrangements do not displace the signal. *Since the probability of this last arrangement is twice that of either of the other two, the middle peak of the triplet is twice as intense.*

The proton of the —$CHBr_2$ group of 1,1,2-tribromoethane (Br_2CHCH_2Br) is an example of a proton of the type having two equivalent protons on an adjacent carbon. the signal from the —$CHBr_2$ group appears as a 1:2:1 triplet and as we would expect, the signal from the —CH_2Br group of 1,1,2-tribromoethane is split into a 1:1 doublet by the proton of the —$CHBr_2$ group.

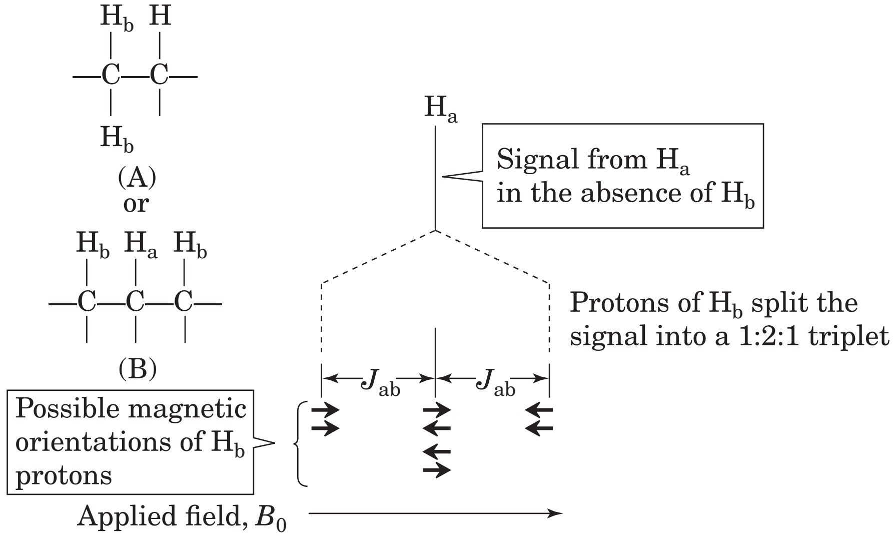

H_b H
—C—C—
H_b
(A)
or
H_b H_a H_b
—C—C—C—
(B)
H_a
Signal from H_a in the absence of H_b
Protons of H_b split the signal into a 1:2:1 triplet
J_ab
J_ab
Possible magnetic orientations of H_b protons
Applied field, B_0

Figure 4.22 **Splitting pattern of a proton signal by the two adjacent equivalent protons**

The spectrum of 1,1,2,3,3-pentachloropropane ($Cl_2\overset{(b)}{C}\overset{(b)}{H}\overset{(a)}{C}\overset{(a)}{H}Cl\overset{(b)}{C}\overset{(b)}{H}Cl_2$) is similar to that of 1,1,2-tribromoethane in that it also consists of a 1:2:1 triplet and a 1:1 doublet. The two H_b atoms of 1,1,2,3,3-pentachloropropane are equivalent even though they are on separate carbon atoms. The NMR spectrum of this compound is given in Figure 4.23.

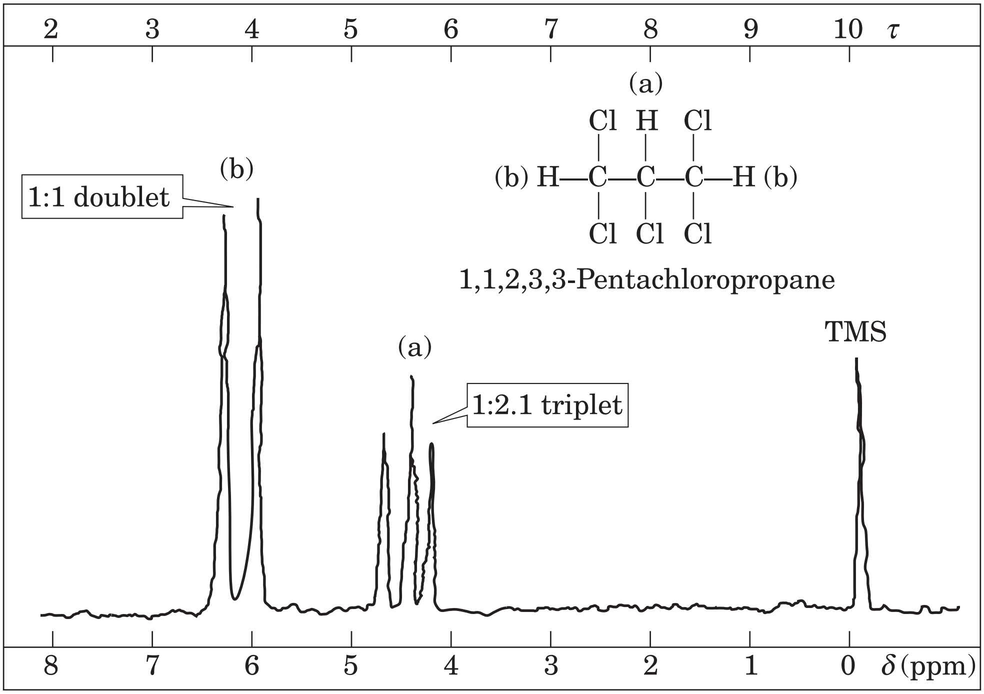


Figure 4.23 **NMR spectrum of 1,1,2,3,3-pentachloropropane**

Three equivalent protons (H_b) on a neighbouring carbon split the signal from H_a into a 1:3:3:1 quartet. This pattern is shown in Figure 4.24:

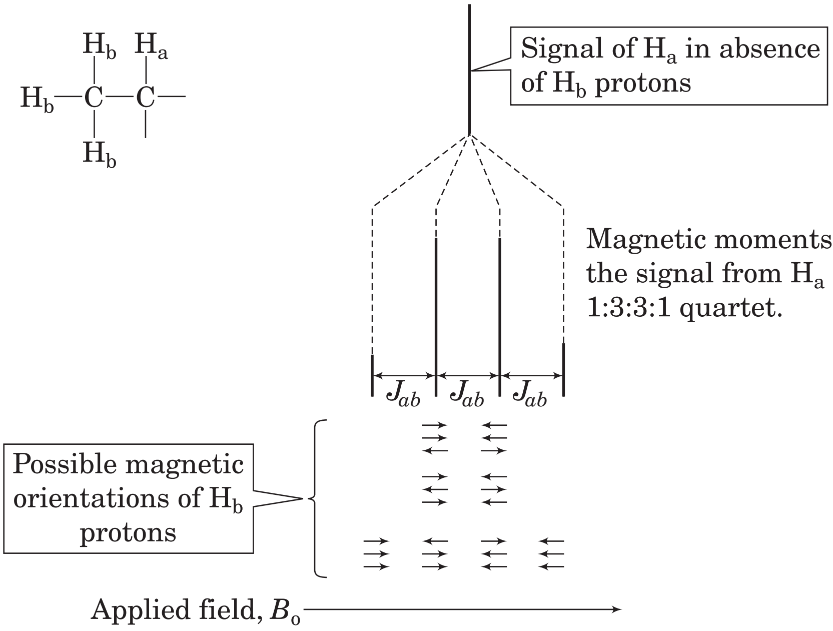

H_b H_a
H_b—C—C—
H_b
Signal of H_a in absence of H_b protons
Magnetic moments of H_b split the signal from H_a into a 1:3:3:1 quartet.
J_{ab}
J_{ab}
J_{ab}
Possible magnetic orientations of H_b protons
Applied field, B_o

Figure 4.24 Splitting pattern of a proton signal by the three adjacent equivalent protons

The signal from two equivalent protons of the —CH_2Br group of ethyl bromide (CH_3CH_2Br) appears as a 1:3:3:1 quartet because of this type of signal splitting. The three equivalent protons of the CH_3— group are split into a 1:2:1 triplet by the two protons of the —CH_2Br group. The NMR spectrum of this compound is given below (Figure 4.25):

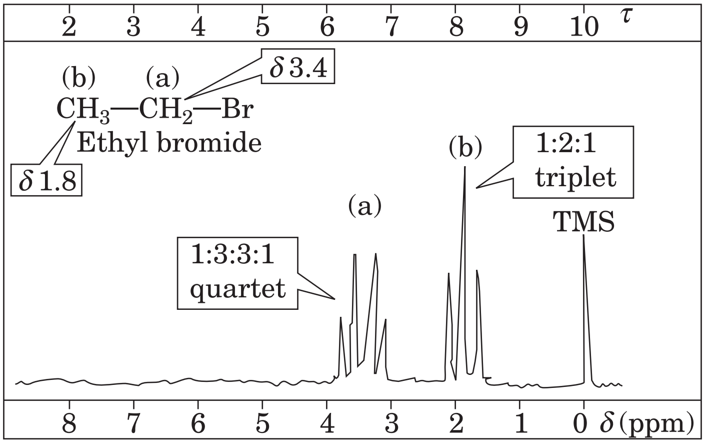


Figure 4.25 NMR spectrum of ethyl bromide

From the analysis above it is clear that if there are n equivalent protons on adjacent atoms these will split a signal into $n + 1$ peaks. This is what is called the $n + 1$ rule.

In all of the NMR spectra that we have considered so far, our attention has been restricted to signal splitting arising from interactions of only two sets of equivalent protons on adjacent atoms. What kind of patterns should we expect from compounds in which more than two sets of equivalent protons interact? This may be well illustrated by the following examples. Let us consider 1-nitropropane ($CH_3^a—CH_2^b—CH_2^c—NO_2$). The methyl protons are spin-spin coupled only to the two protons of the $—CH_2^b—$ group. Therefore, the methyl protons appear as a triplet. The $—CH_2NO_2$ protons are coupled only to the two protons of the $—CH_2^b—$ group and therefore, they appear as a triplet. Although the vicinal hydrogens of the $—CH_2^b—$ group are different and have different chemical shifts, they are combined to give n because $J_{ab} = J_{bc}$. For this reason, H_b appears as a sextet (5 + 1 = 6). This becomes clear from Figure 4.26:

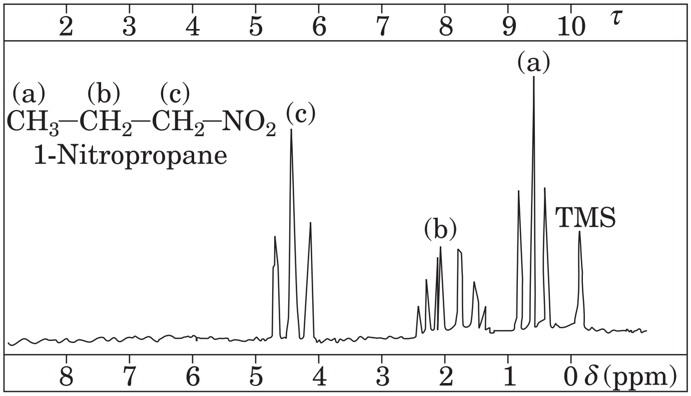


Figure 4.26 NMR spectrum of 1-nitropropane

When, however, the coupling constants are different, the vicinal hydrogens cannot be added and each kind of vicinal hydrogens couples independently with the hydrogen in question. Therefore, in $(CH_3^a)_2CH^bCH^cClCH^dCl_2$ (1,1,2-trichloro-3-methylbutane), the splitting of the signal for the H^c proton occurs by the H^b and H^d protons and results in formation of a doublet of doublets (Figure 4.27).

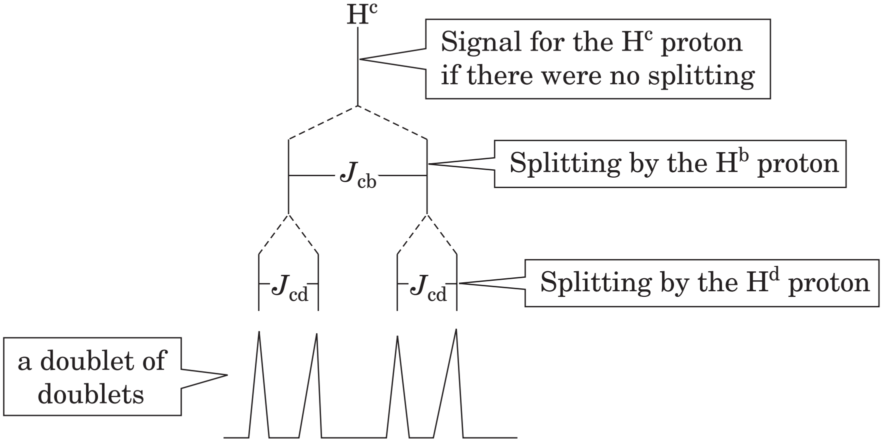
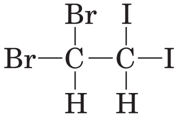
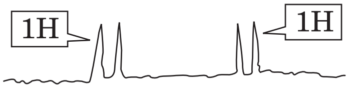
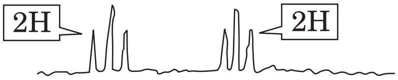
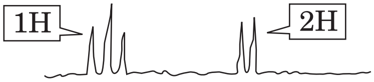
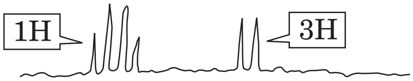
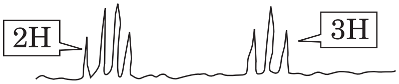
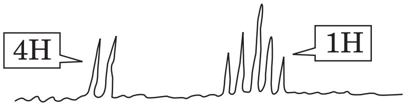
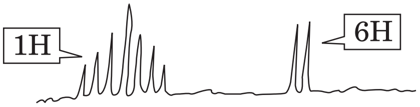

Hᶜ
Signal for the Hᶜ proton if there were no splitting
J_cb
Splitting by the Hᵇ proton
J_cd
J_cd
Splitting by the Hᵈ proton
a doublet of doublets

Figure 4.27 A splitting diagram for a doublet of doublets. The diagram starts with J_{cb} because $J_{cb} > J_{cd}$

Some commonly encountered spin-spin splitting patterns are given in Table 4.10.

Table 4.10 Examples of commonly observed splitting patterns

	Compound		Splitting patterns
1.	 $\mathrm{Br{-}\overset{Br}{\underset{H}{C}}{-}\overset{I}{\underset{H}{C}}{-}I}$	⇒	 Two doublets of equal intensity
2.	$Br{-}CH_2{-}CH_2{-}Cl$	⇒	 Two triplets of equal intensity
3.	$Br_2CH{-}CH_2Br$	⇒	 A triplet and a doublet
4.	Cl_2CHCH_3	⇒	 A quartet and doublet
5.	$ClCH_2CH_3$	⇒	 A quartet and a triplet
6.	$ClCH_2CHBrCH_2Cl$	⇒	 a doublet and a quintet
7.	$CH_3CHClCH_3$	⇒	 A septet and a doublet Downfield ⟷ Upfield high ν ⟷ low ν

Relative intensities of peaks in a multiplet: The relative intensities of the peaks of a multiplet depends on n, the number of neighbouring equivalently coupled protons. We have seen that doublet (n = 1) peaks are in the ratio 1:1, triplet peaks are in the ratio 1:2:1, and quartets are in the ratio 1:3:3:1. Therefore, the relative intensities of peaks within a multiplet may be given by coefficients of the binomial expression $(a + b)^n$. When this expression is expanded to the desired value of n, the coefficients give the relative intensities. For example, when $n = 2$, $(a + b)^2 = a^2 + 2ab + b^2$, the signal would be a triplet with intensities of lines, 1:2:1. Similarly, when $n = 3$, $(a + b)^3 = a^3 + 3a^2b + 3ab^2 + b^3$, the signal would be a quartet and the intensities of lines are 1:3:3:1. The multiplicity and relative intensities may be easily obtained from Pascal's triangle. Each number between the terminal 1's of a multiplet is obtained by adding the pair of numbers directly above in the preceding multiplet. See examples shown with dashed lines.

n (Number of equivalent protons responsible for splitting)	Multiplicity of observed signals	Relative intensity and line distribution within the multiplet
0	Singlet	1
1	Doublet	1 : 1
2	Triplet	1 : 2 : 1
3	Quartet	1 : 3 : 3 : 1
4	Quintet	1 : 4 : 6 : 4 : 1
5	Sextet	1 : 5 : 10 : 10 : 5 : 1

4.4.11 Coupling Constant

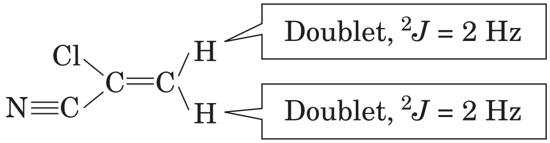
It must be remembered that all these spin-spin splitting are reciprocal. In the NMR spectrum of 1,1,2-tribromoethane (Br_2CHCH_2Br), for example, the single proton appears as a triplet, the two protons appear as a doublet, and the separation between the three peaks of triplet is exactly the same as the separation of the two peaks of the doublet.

The distance between peaks in a multiplet is a measure of the effectiveness of spin-spin coupling, and is called the *coupling constant*, J. The value of the coupling constant (measured in Hz) remains the same, whatever the applied magnetic field (that is, whatever the radio frequency used). In this respect, spin-spin splitting differs from chemical shift, and when necessary, the two can be distinguished by running the spectrum at a different radio frequency. The value of chemical shifts in Hz will change, whereas peak separations due to splitting remain constant. (When divided by the radio frequency and thus converted into ppm, the numerical value of the chemical shift would of course, remain constant.)

Coupling constant depends markedly on the structural relationships between the coupled protons. The number of bonds intervening between the coupling nuclei is important because the coupling is transmitted via the electrons of these bonds. It is a convenient notation to indicate this number as a superscript to the symbol J. Therefore, direct coupling (e.g., coupling of a proton with an attached carbon-13 nucleus, $^{13}C—^{1}H$) would be a one-bond coupling, ^1J; the coupling between the two protons on a $—CH_2—$ group would be symbolized by ^2J; that between protons on adjacent carbon as ^3J, and so on.

1. *Geminal coupling:* In alkanes and other molecules with relatively free rotation about C—C σ bonds, H atoms bonded to the same C atom in $—CH_2—$ and $—CH_3$ groups are generally equivalent because of the rapid bond rotation. An exception is when a $—CH_2—$

is adjacent to a chirality centre. However, when there is restricted bond rotation, as in alkenes or cyclic structures, H atoms bonded to the same C atom may not be equivalent, especially if the molecule is not symmetrical. Nonequivalent protons on the same C atom will couple to each other and cause splitting. This is what is called *geminal coupling*. Geminal coupling constants (^2J) involving protons on $=CH_2$ groups are generally small (in the order of 0 to 5 Hz). In 1-chloro-1-cyanoethene, for example, the two hydrogens being diastereotopic appear as a pair of doublets. The splitting in each doublet is 2 Hz.



1-Chloro-1-cyanoethene

However, geminal coupling, involving protons on $—CH_2—$ groups, is strong, ^2J being typically 10–18 Hz.

Splitting due to geminal coupling is seen only when the two protons are diastereotopic.

2. *Vicinal coupling:* It varies from $^3J = 0$ to $^3J = 12$ Hz in regid systems, but in freely rotating carbon chains (alkyl groups) it is usually around 8 Hz. Coupling between protons on vicinal carbon atoms depends primarily on the dihedral angle ϕ between planes of two σ C—H bonds. It is maximum if ϕ is 0° or 180° and zero or minimum when it is 90°. The relation between the coupling constant and dihedral angle between the two C—H bonds has been established theoretically and may be depicted in form of familiar **Karplus Curve** (Figure 4.28).

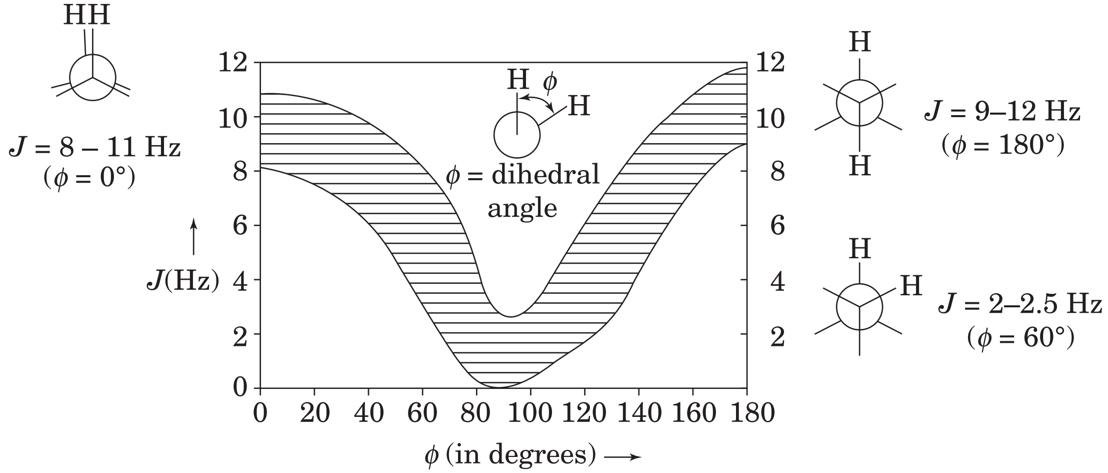
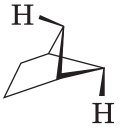


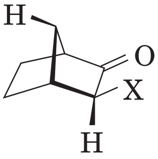
Figure 4.28 Karplus curve

The variation of coupling constant as a function of dihedral angle, ϕ, may be explained on the basis of interaction between the vicinal C—H orbitals. Strong interaction between $\sigma_{C—H}$ orbital in vicinal position is expected when the dihedral angle, $\phi = 0°$, whereas there is no interaction when the σ_{C-H} orbitals are orthogonally oriented (ϕ = 90°). When ϕ = 180°, much stronger interaction is expected between one σ_{C-H} orbital with one σ^*_{C-H} orbital.

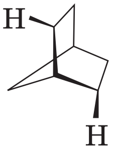
3. *Long-range coupling:* Since the coupling information is relayed through the intervening covalent bonds, the magnitude of J diminishes rapidly with increase in the number of intervening bonds and *it is almost negligible if more than three bonds intervene between the coupling protons*. Therefore, ^3J is observed but ^4J is not (actually it is vanishingly small). Long-range coupling (^4J) is observed within rigid systems in which the four σ-bonds are oriented in the form of W. The W effect is well illustrated by the following compounds:



^4J = 7 Hz

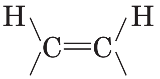


^4J = 3 Hz

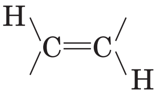


^4J = 1 Hz

4. *Trans and cis coupling: Trans* coupling in alkene system (^3J = 11–19 Hz) is stronger than *cis* coupling (J = 5–14 Hz). Typical values are 16 and 8 Hz, respectively.



cis
J = 5–14 Hz

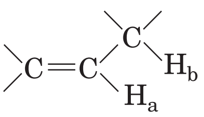


trans
J = 11–19 Hz

[In *trans* alkenes (ϕ = 180°), there occurs strong interaction between one σ_{C-H} orbital and the other σ^*_{C-H} orbital, and so, the coupling is relatively large.]

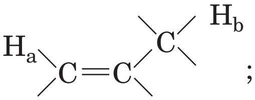
5. *Aromatic coupling:* It depends on whether the coupling protons are *ortho*, *meta* or *para* to each other, and in simple cases the orientations can be decided by coupling content values ($^3J_{ortho}$ = 7–10 Hz, $^4J_{meta}$ = 2–3 Hz and $^5J_{para}$ = 0–1 Hz).

Some other important coupling constant values:



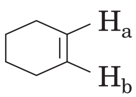
;

$^3J_{ab}$ = 4–10 Hz

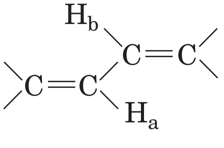


;

$^4J_{ab}$ = 0–2 Hz
(allylic coupling)

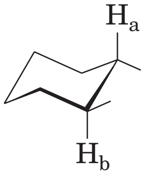


J_{ab} = 8–11 Hz

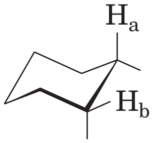


;

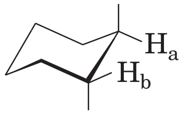
$^3J_{ab}$ = 10–13 Hz



J_{ab} = 10–13 Hz
(axial–axial)



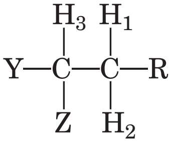
J_{ab} = 2–5 Hz
(axial–equatorial)



J_{ab} = 2–5 Hz
(equatorial–equatorial)

4.4.12 Chemical Shift Equivalence and Magnetic Equivalence

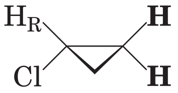
The NMR equivalence or nonequivalence, i.e., magnetic equivalence or nonequivalence of various protons is reflected by two NMR parameters: chemical shift and coupling constant. In order for two protons to be identical in the NMR, i.e., to magnetically equivalent they must (a) have the same chemical shift and (b) be spin-coupled equally to all other nuclei within the molecule. Only chemical shift equivalent protons may be coupling constant equivalent, i.e., *the test for magnetic equivalence is valid only when two protons are chemical shift equivalent*. Chemical shift nonequivalent diastereotopic protons always exhibit coupling constant nonequivalence, i.e., *diastereotopic protons are magnetically nonequivalent*. For example, in the following compound, H_1 and H_2 will couple to H_3. However, the coupling between H_1 and H_3 ($J_{1,\ 3}$) will not be identical to the coupling between H_2 and H_3 ($J_{2,\ 3}$) and as a result, each of these protons will split H_3 differently. Since H_1 and H_2 are coupled differently to a third proton (H_3), they are coupling constant nonequivalent. Since they are diastereotopic, they are chemical shift non-equivalent.

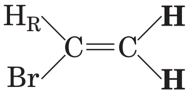


$$\begin{array}{ccccccc} & & H_3 & & H_1 & & \\ & & | & & | & & \\ Y & - & C & - & C & - & R \\ & & | & & | & & \\ & & Z & & H_2 & & \end{array}$$

$(J_{1,3} \neq J_{2,3})$

The boldface protons in the following compounds are also chemical shift as well as coupling constant nonequivalent.

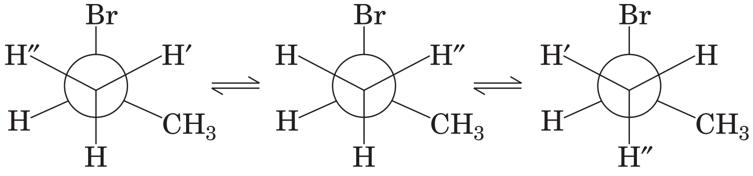




(H_R is the reference proton to which the other two are coupled unequally.)

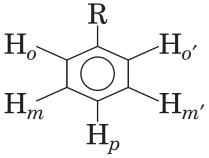
The six methyl protons in isopropyl bromide or 2-bromopropane ($CH_3CHBrCH_3$) are both chemical shift as well as coupling constant equivalent. All the six protons of the two methyl groups are chemically equivalent. Therefore, they have the same chemical shifts. Assuming no rotation about the C—C bond, each of these three methyl hydrogens (H, H′ and H″) is in a different molecular environment and for one methyl group NMR will show the presence of three different hydrogens. However, this is not the case. Due to rapid rotation, the NMR spectrometer records an average environment for all the six hydrogens which display the same chemical shift and all of them give one signal that split into a doublet by the proton on the carbon bearing bromine. Again, if it is assumed that there occurs no rotation around the C—C bond, coupling, e.g., of H′ with H and H″ with H would be different (different dihedral angles). Then it can be said that the protons H′ and H″ are chemically equivalent but magnetically nonequivalent. However, again due to fast rotation the methyl protons have equal coupling to the proton on carbon bearing bromine on average and become magnetically equivalent.

$(CH_3)_2\,CH—Br$
Isopropyl bromide



Stable conformations of isopropyl bromide

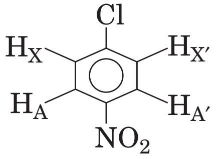
In a monosubstituted benzene, C_6H_5—R, the protons that are adjacent to R, i.e., the *ortho* protons (H_o and $H_o{}'$ are in the same environment and therefore, they have the same chemical shift. However, they are disposed differently relative to a *meta* proton, say H_m and are, therefore, coupling constant nonequivalent. Thus, it is possible to have protons that are chemical shift equivalent but coupling constant nonequivalent. This situation leads to more spin-spin splitting than would have been imagined had only chemical shift equivalence been considered.



(H_o and $H_{o'}$ have the same chemical shift but different coupling constant.)

(A monosubstituted benzene)

Also, in a *p*-disubstituted benzene, e.g., *p*-chloronitrobenzene, the protons *ortho* to the nitro group (H_A and $H_{A'}$) are chemical shift equivalent to each other and the protons *ortho* to chlorine (H_x and $H_{x'}$) are also chemical shift equivalent to each other.

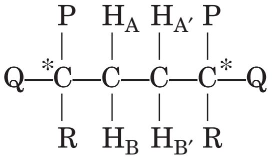


p-Chloronitrobenzene

In general, for *p*-disubstituted benzene rings, J_{AX} and $J_{A'X'}$ are the same, approximately 7–10 Hz; $J_{A'X}$ and $J_{AX'}$ are also the same but much smaller, approximately 0–1 Hz. Since H_A and $H_A{}'$ couple differently to another specific proton (i.e., H_X or $H_{X'}$), they are not magnetic equivalent and first-order rules do not apply. Similarly, H_X is not magnetic equivalent to $H_{X'}$. The system is described as AA′XX′ and the spectrum is very complex. Fortunately, the pattern is readily recognized because of its symmetry and apparent simplicity.

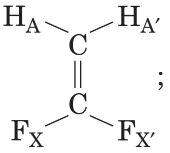
Aromatic protons of symmetrically *ortho*-substituted benzenes also give AA′BB′ spectra. An example is *o*-dichlorobenzene.

Chemical shift equivalent protons exhibiting coupling constant nonequivalence receive identical letter designations, since the letter refers only to chemical shift. However, to distinguish coupling constant nonequivalence, the letter is ‘primed’. This is illustrated below for the AA′BB′ and AA′XX′ systems. [When the methylene protons adjacent to a chiral centre have only slightly different chemical shifts, they are represented as an AB system and not as an AX system. However, when the difference in chemical shift is considerable, it represents an AX system.]

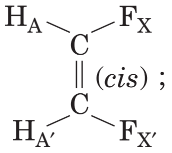


I

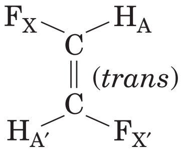
AA′BB′ spin system



II



III

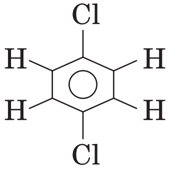


IV

AA′XX′ spin systems

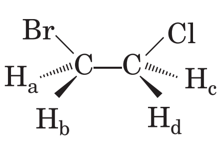
In I, H_A and $H_{A'}$ have identical chemical shifts but couple differently to H_B (or $H_{B'}$), while H_B and $H_{B'}$ have identical chemical shifts but couple differently to H_A (or $H_{A'}$). In II, III and IV, H_A and $H_{A'}$ have identical chemical shifts but couple differently to either flurine (F_X or $F_{X'}$). [^1H and ^{19}F do split one another in the same way that ^1H and ^1H split one another, except that *J* is larger for the former coupling.]

Compounds which have identical *p*-substituents, e.g., *p*-dichlorobenzene, display single line spectra. Due to molecular symmetry all the four ring protons are chemical shift equivalent. Also, they are magnetically equivalent.

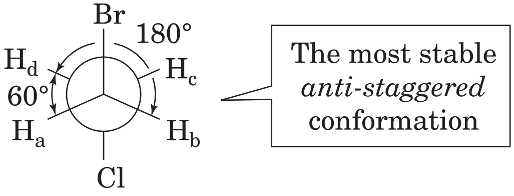


p-Dichlorobenzene

In 1-bromo-2-chloroethane, the two protons H_a and H_b (or H_c and H_d) are coupling constant nonequivalent but chemical shift equivalent.



1-Bromo-2-chloroethane



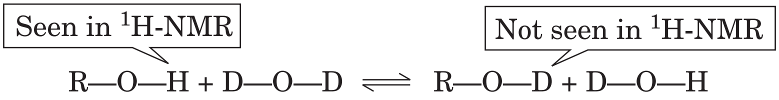
The most stable *anti-staggered* conformation

This is due to the fact that coupling constant depends on the dihedral angle between the two vicinal protons. The most stable conformation of this compound is the *anti-staggered* conformation as shown above. The dihedral angle between H_a and H_d is 60° and that between H_b and H_d is 180° and so *J* for the latter is larger than for the former (*J* is largest when the angle is 0° or 180° and very small or zero when the angle is 90°). Hence, H_a and H_b are coupling constant nonequivalent, i.e., they are magnetically nonequivalent.

4.4.13 Deuterium Exchange Reactions

It has been found that if a few drops of deuterium oxide (D_2O) are added in the sample, D_2O exchanges with the abile protons such as —OH, —NH_2, —SH and also with the reactive methylene protons flanked by the two carbonyl groups (e.g., $CH_3COCH_2COCH_3$). The mechanism involves the same course as is seen in proton exchange reactions.

When a little D_2O is added to ROH, then due to rapid exchange, ROH becomes ROD.



Seen in ^{1}H-NMR

Not seen in ^{1}H-NMR

$$\text{R—O—H} + \text{D—O—D} \rightleftharpoons \text{R—O—D} + \text{D—O—H}$$

Thus, the signal for OH proton normally observed in ROH will be missing in the NMR spectrum (because deuterium does not resonate under the conditions used for hydrogen) and instead, a signal for proton in H—OD will appear. Similarly, if a little D_2O is added to RCOOH, then due to rapid exchange, it becomes RCOOD.

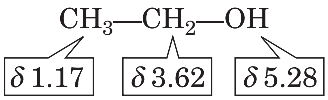
$$\text{RCOOH} + D_2O \rightleftharpoons \text{RCOOD} + \text{HOD}$$

Clearly, the signal for the proton in RCOOH (δ 10.5–12) will disappear and a signal for the proton corresponding H—OD will appear instead. This technique which is usually employed for detecting the presence of groups like —OH, —NH_2, etc. is called *deuteration*.

4.4.14 Interpretation of NMR Spectra of Some Representative Compounds

NMR spectrum of a compound provides some important information about its molecular structure. The **position of signals**, i.e., the **chemical shift values** tell us about the electronic environment of each kind of proton. The **number of signals** tells us how many kinds of protons in different chemical environments are present in the molecule. The **intensities of different signals** tell us about the relative number of protons of different kinds, the **multiplicity of signal** tells us the number of protons bonded to adjacent carbons, and the **coupling constants** (J) identify the coupled protons. Using these informations we can predict the structure of a compound.

1. NMR spectrum of ethyl alcohol (CH_3CH_2OH)



$$CH_3\text{—}CH_2\text{—}OH$$

In the NMR spectrum of pure ethanol, three signals appear at δ1.17 (as a triplet), δ3.62 (as a multiplet) and δ5.28 (as a triplet) respectively. From the heights of the integration lines it becomes clear that the ratio of the number of protons is 3:2:1. The signal at δ5.28 is due to the OH proton, the proton attached to the highly electronegative oxygen atom. The signal is split into a triplet (J = 6Hz) due to spin-spin coupling with the two methylene (—CH_2—)

protons. The signal at δ 1.17 is due to three methyl protons. The signal is split into a triplet (J = 8 Hz) because of spin-spin coupling with the adjacent methyl (—CH_2—) protons. The signal at δ 3.62 is due to the methylene (—CH_2—) protons. Since the methylene carbon is attached to the electronegative oxygen atom, these two protons appear at somewhat downfield compared to methyl protons. The signal appears as a multiplet because of spin-spin coupling of these two protons with both the CH_3 protons and the OH proton. Due to coupling with methyl proton, a quartet (J = 8Hz) is formed first and then each of the four peaks are split into a doublet (J = 6 Hz) due to coupling with the OH proton and this results in formation of an octet.

If ethanol contains some impurity (acidic or basic), the CH_3 protons appear as a triplet (δ 1.17), CH_2 protons appear as a quartet (σ 3.62) and the OH proton appears as a singlet (δ 5.30). In the presence of impurities, the OH proton undergoes rapid **chemical exchange** (i.e., the molecules exchange their OH proton rapidly) which causes **spin decoupling**. This matter is already discussed in **article no. 4.4.8**.

When the spectrum of ethanol is taken by adding a little D_2O into it, the signal due to OH proton disappears because H is displaced by D, which does not resonate under the conditions used for hydrogen.

$$C_2H_5OH + D_2O \rightleftharpoons C_2H_5OD + HOD$$

The NMR spectrums of pure ethanol (Figure 4.29), impure ethanol (Figure 4.30) and after D_2O exchange (Figure 4.31) are given below:

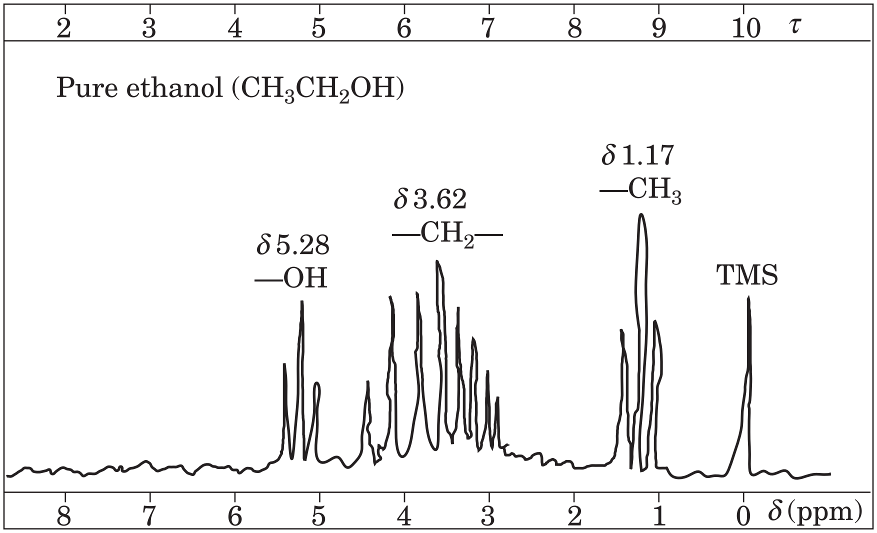


Figure 4.29 NMR spectrum of pure ethanol

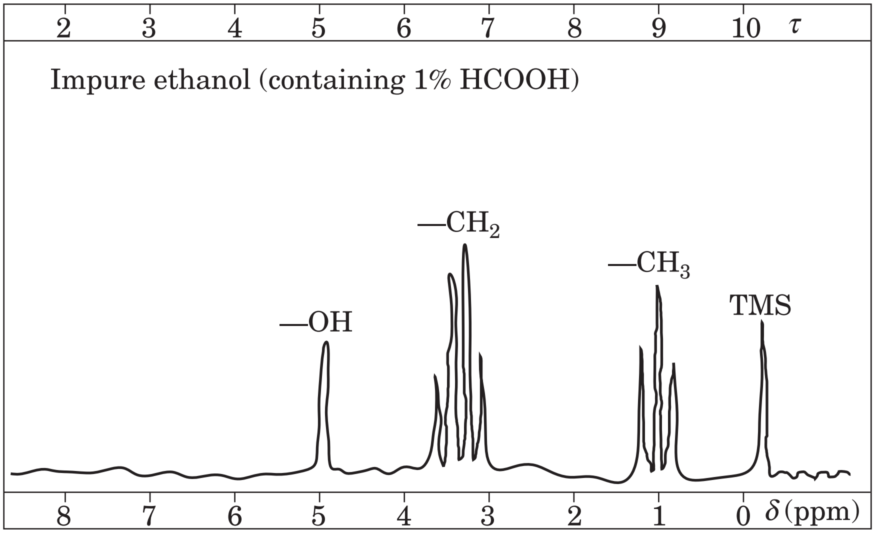


Figure 4.30 NMR spectrum of impure ethanol

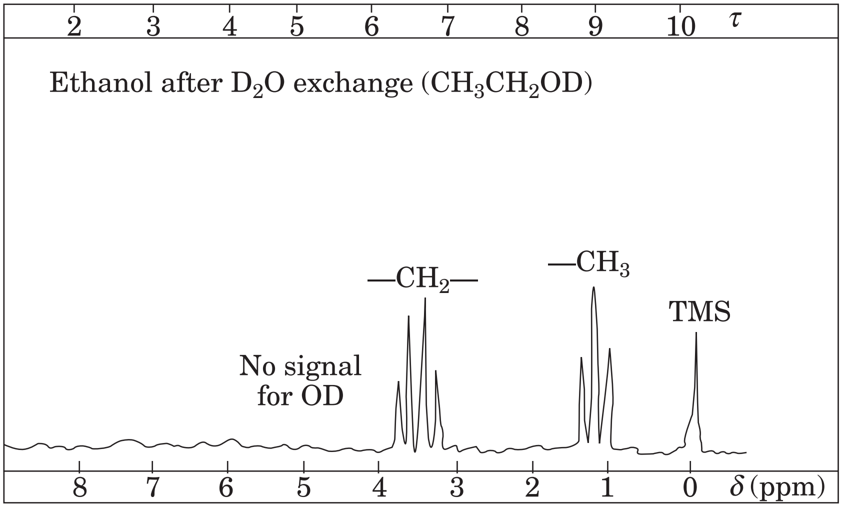


Figure 4.31 NMR spectrum of ethanol after D_2O exchange

2. NMR spectrum of 2-chloropropanoic acid ($CH_3CHClCO_2H$)

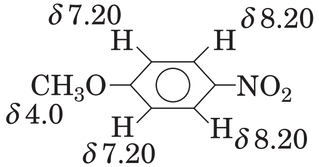
$$\overset{3}{CH_3}\text{—}\overset{2}{CHCl}\text{—}\overset{1}{CO_2H}$$
$$\delta\,1.8 \quad \delta\,4.50 \quad \delta\,13.0$$

In the NMR spectrum of 2-chloropropanoic acid, three signals appear at δ 13.0 (as a singlet), δ 4.50 (as a quartet) and δ 1.80 (as a doublet) respectively. From the heights of the integration lines it becomes evident that the ratio of the number of protons is 1:1:3. The signal at δ 13.0 (much downfield) is due to the COOH proton. The signal appearing at δ 4.50 is due to the proton at C-2. It appears somewhat downfield because the carbon is attached to an electronegative Cl atom and an electron-attracting —COOH group. The signal is split into a quartet because of spin-spin splitting with the three methyl protons. The signal appearing at δ 1.80 is due to the three methyl protons; it is split into a doublet because of spin-spin coupling with the C-2 proton.

When the spectrum is taken in the presence of D_2O, the signal at δ 13.0 disappears because of displacement of —COOH proton by D.

$$CH_3CHClCOOH + D_2O \rightleftharpoons CH_3CHClCOOD + HOD$$

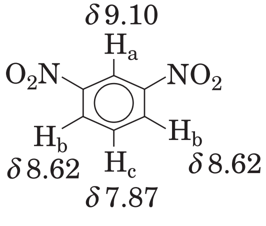
3. NMR spectrum of p-nitroanisole (*p*-MeO$C_6H_4NO_2$)



In the NMR spectrum of *p*-nitroanisole, three signals appear at δ 4.0 (as a singlet), δ 7.20 (as a doublet) and δ 8.20 (as a doublet), respectively, and the ratio of the number of protons at these positions is 3:2:2. The signal at δ 4.0 is due to the three —OCH_3 protons. The signal remains unsplit due to lack of required proton. The signal at δ 7.20 is due to two ring protons *ortho* to the electron-donating (+R) methoxy group (somewhat upfield compared to benzene protons). The signal is split into a doublet (J = 10 Hz) since these protons undergo spin-spin coupling with the protons *ortho* to the —NO_2 group. The signal at δ 8.20 is due to the two ring protons *ortho* to the electron-withdrawing (by —I and —R effects) —NO_2 group. This signal is also split into a doublet (J = 10 Hz) due to spin-spin coupling with protons *ortho* to the —OCH_3 group.

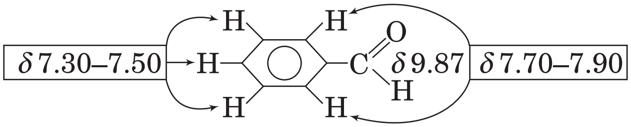
Although the protons *ortho* to —NO_2 (or —OCH_3) group are chemically equivalent, they are not magnetically equivalent and for this reason, a closer look shows many small splitting.

4. NMR spectrum of *m*-dinitrobenzene (*m*-$O_2NC_6H_4NO_2$)



In the NMR spectrum of *m*-dinitrobenzene, three signals appear at δ 9.1 (as a triplet), δ 7.87 (as a triplet) and δ 8.62 (as a double doublet, i.e., quartet) and the proton ratio is 1:1:2. The much downfield signal at δ 9.10 is due to the H_a proton which is strongly deshielded by the two strong electron-withdrawing —NO_2 groups. The signal is split into a triplet due to spin-spin coupling with the H_b protons (small meta coupling). The signal at δ 7.87 is due to the H_c proton which is split into a triplet by the two H_b protons (large *ortho* coupling; *para* coupling is less important). The signal at δ 8.62 is due to the two H_b protons. The signal is split by the H_c proton (large *ortho* coupling) and by the H_a proton (small *meta* coupling) and appears as a double doublet, i.e., quartet.

5. NMR spectrum of benzaldehyde (C_6H_5CHO)



Benzaldehyde

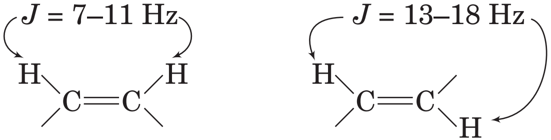
A look at the NMR spectum of benzaldehyde reveals the following three signals: (i) a 3H multiplet from δ 7.30 to 7.50, (ii) a 2 H multiplet from δ 7.70 to 7.90 and (iii) a 1H singlet at δ 9.87. The 3 H multiplet from δ 7.30 to 7.50 is due to the two *meta* and one *para* proton of the ring. The 2 H multiplet from δ 7.70 to 7.90 is due to the two *ortho* protons of the ring. The much downfield shift of these two protons is attributed to the anisotropic effect of the carbonyl group in addition to the electron-withdrawing –I and –R effect of the —CHO group. The 1 H singlet at δ 9.87 is due to the typical aldehydic proton.

4.4.15 Applications of NMR Spectroscopy

Out of various spectroscopic techniques, the NMR spectroscopy is the most important one. Some of the applications of this very much popular technique are given below:

1. Determination of structure: The following different features of NMR spectrum provide a detailed information about the structure of an unknown compound: (i) the chemical shift values, (ii) the number of signals, (iii) characteristic pattern of splitting (d, t, q, etc.), (iv) coupling constant values and (v) integral ratios. For example, a 3H, t and a two H, q (J = 7.0 Hz in each case) clearly establishes the presence of ethyl group (CH_3CH_2—) in the molecule. Some other techniques like *deuterium labelling, double resonance*, etc. are also much useful in elucidating the structure of organic compounds.

2. Distinction between geometric or *cis-trans* isomers: The *cis-* and *trans*-isomers of a compound can be easily distinguished by the values of the coupling constant which is 7–11 Hz in the case of *cis-* protons and 13–18 Hz in the case of *trans*-protons.



cis *trans*

3. Distinction between inter- and intramolecular hydrogen bonding: The H atom involved in H-bonding is deshielded because of attraction of electrons around this hydrogen by the electronegative O or N atom of other molecule. The extent of deshielding depends upon the strength of H-bond which in turn depends upon the concentration, temperance and nature of the solvent. Intramolecular hydrogen bonding also shifts the absorption downfield. The two types of H-bonding can be distinguished as the intramolecular H-bonding is not concentration dependent.

4. Identification of reaction products: The NMR spectroscopy can be used to identify the actual product in a reaction in which two or more products are possible. For example, either of the products I or II can be obtained in the following addition reaction:

$$CH_3CH{=}CH_2 \xrightarrow{HBr} \underset{I}{CH_3CH_2CH_2Br} + \underset{II}{CH_3CHBrCH_3}$$

The spectrum of I would show three signals, whereas that of II would show two signals. The spectrum of the product is found to be identical with that of II. Therefore, the product is $CH_3CHBrCH_3$ (obtained according to the Markownikoff's rule).

5. Quantitative analysis (determination of relative amounts of tautomers): The percentages of *keto* and *enol* forms in an equilibrium mixture can be determined quantitatively by using NMR spectroscopy. For example, the NMR spectra of acetylacetone (a (β-diketone) exhibits distinct signals due to —CH_2— protons of the keto form and —CH═ proton of the enol form. The percentages of these two forms can be easily calculated by comparing the areas under these signals (integral areas). The spectrum of acetylacetone reveals that the signal due to —CH_2— protons of the keto form appearing at δ 3.57 shows the integral area of 1.33 divisions and that due to —CH═ proton of the enol form appearing at δ 5.50 shows the integral area of 2.66 divisions. Hence, the integral area of two enolic protons = $2 \times 2.66 = 5.32$ divisions and the total integral area of —CH_2— protons = $1.33 + 5.32 = 6.65$ divisions. Hence, the equilibrium mixture contains $\frac{1.33}{6.65} \times 100$ or 20% keto form and $\frac{5.32}{6.65} \times 100$ or 80% enol form.

SOLVED PROBLEMS

1. What property must a nucleus have to exhibit nuclear magnetic resonance, i.e., to be NMR active?

Solution Any atomic nucleus that has an odd mass number, an odd atomic number, or both (or simply if the nucleus have an odd number of protons and/or neutrons) exhibits nuclear magnetic resonance, and it is said to be NMR active.

2. Which of the following atoms are not NMR active?

$$^{15}N,\ ^{13}C,\ ^{32}S,\ ^{31}P,\ ^{12}C,\ ^{11}B,\ ^{2}H,\ ^{14}N,\ ^{19}F,\ ^{16}O$$

Solution Inactive atoms have even number of protons and neutrons. These atoms are, therefore, ^{12}C(6*p*, 6*n*), ^{16}O (8*p*, 8*n*) and ^{32}S (16*p*, 16*n*)

3. All hydrogens in a molecule do not undergo spin-flip at the same applied magnetic field at constant frequency—Why?

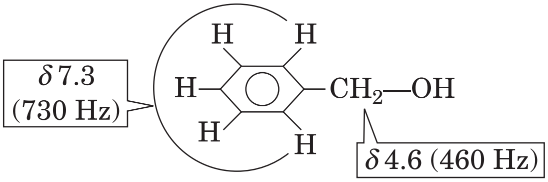
Solution At the fixed radio frequency of the NMR spectrometer, all hydrogens require the same field strength to spin-flip. However, the magnetic field 'felt' by a proton is not necessarily only that which is applied by the magnet, because the electrons in the bond to the H atom and those in nearby π bonds induce their own magnetic fields. This induced field partially shields the proton from the applied field B_0 and so, the applied field must then be increased. The larger the shielding effect, the greater must be the applied field for resonance to occur. As shielding decreases, the applied field required for resonance to occur decreases. When the induced field actually deshields the proton, a smaller applied field is required for spin-flip. In this situation, the effective field is actually the some of the applied and induced fields. Therefore, the applied field decreases with increase in the magnitude of the induced field.

4. **The OH signal is shown in an NMR spectrum at 144 Hz higher frequency (downfield) than TMS. Calculate the chemical shift in terms of δ. (The TMS frequency is 60 MHz.)**

Solution $\delta = \frac{144 \text{ Hz}}{60 \text{ MHz}}$ ppm = 2.40 ppm

5. **What is the chemical shift position (in δ units) for the CH_2 and ring protons of benzyl alcohol ($PhCH_2OH$) in a spectrum recorded on a 100 MHz instrument?**

Solution



6. **How many hertz does 1 ppm (one unit on the scale) correspond to on an instrument recording proton signal at (a) 60 MHz, (b) 250 MHz and (c) 300 MHz?**

Solution (a) 60 Hz; (b) 250 Hz and (c) 300 Hz

7. **What do you mean by the terms (a) downfield and (b) upfield used in NMR spectra?**

Solution To generate an NMR spectrum, the magnetic field strength, B_0, is increased from left to right. (a) The less shielded and the more deshielded proton signals appear *downfield* at the lower field, which is the left hand side of the spectrum. (b) The more shielded proton signals appear *upfield* at the higher field, which is the right-hand side of the spectrum.

8. **Explain why TMS (Me_4Si) is used as internal standard in NMR spectral studies.**

Solution TMS (tetramethylsilane) is relatively inert and has no polar group. It is highly volatile (b.p. 25.5°C). So it can be easily removed after use, making the recovery of the sample easy. It is miscible with almost all of the organic solvents and does not form any complex with them. It contains only one type of protons and so, it gives only one sharp peak. Also, the signal due to TMS protons appears outside the normal range of protons of most of the organic compounds. Therefore, TMS fulfils all the requirements for a good internal standard and for this reason, it is generally used as an internal standard for NMR studies.

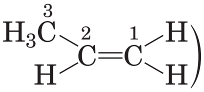
9. How many NMR signals are expected to be found in the NMR spectrum of the following compounds?

(a) $CH_3CH_2CH_2OH$ **(b) $(CH_3)_2CHOCH(CH_3)_2$**

(c) $CH_3COCH_2CH_3$ **(d) $C_6H_5CH_3$**

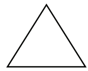
(e) $(CH_3)_2C{=}(CH_3)_2$ **(f) $CH_3CH_2CH_2OCH_2CH_2CH_3$**

(g) $CH_3CH{=}CH_2$

Solution (a) 4 (four types of protons); (b) 2 (two types of protons); (c) 3 (three types of protons); (d) 2 (two types of protons; in fact the aromatic protons are of three types and for this, in high resolution instruments, the five protons show a complex pattern showing up as a multiplet); (e) 1 (one type of proton); (f) 3 (three types of protons); (g) 4 (four types of protons: 

). Protons at C-1 are diastereotopic and so, each of them produces a signal.

10. How would you distinguish between the two compounds in each of the following pairs using NMR spectroscopy?

(a) $CH_3CH{=}CH_2$ and 

I II

(b) CH_3COCH_3 and CH_3CHO

III IV

(c) $CH_3COOCH_2CH_3$ and $CH_3CH_2COOCH_3$

V VI

(d) $HCOOCH_3$ and CH_3COOH

VII VIII

(e) $CH_3C{\equiv}CH$ and $CH_2{=}C{=}CH_2$

IX X

(f) $CH_3CH_2C{\equiv}CH$ and $CH_3C{\equiv}CCH_3$

XI XII

Solution

(a) These two can be differentiated by the number of signals. The compound I produces 3 signals, whereas the compound II produces only one signal.

(b) III ⇒ 1 signal; IV ⇒ 2 signals.

(c) These two can be differentiated by the positions of 3H singlet. In V the signal appears at $\delta \sim 2.10$ and in VI it will appear at $\delta \sim 3.5$ (the —CH_3 group is directly attached to the electronegative oxygen atom).

(d) These two can be differentiated by the positions of 3 H singlet and 1 H singlet. 3 H singlet appears in VII at $\delta \sim 2.10$ and in VIII, at $\delta \sim 3.5$. 1 H singlet appears in VII, at $\delta \sim 9.0$ (—CHO) and in VIII, at $\delta > 11$. This signal in VIII disappears in the presence of D_2O due to exchange with D.

(e) IX ⇒ 2 signals; X ⇒ 1 signal.

(f) XI ⇒ 3 signals; XII ⇒ 1 signal.

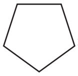
11. The following compounds exhibit only one NMR signal:

(a) C_5H_{10} (b) C_5H_{12} (c) $C_2H_4Cl_2$ (d) C_8H_{18}

(e) $C_3H_6Br_2$ (f) C_3H_4 (g) $C_2H_3Cl_3$

Suggest a structure for each of them

Solution

(a) ; (b) $(CH_3)_4C$; (c) $ClCH_2CH_2Cl$; (d) $(CH_3)_3C—C(CH_3)_3$; (e) $CH_3CBr_2CH_3$

(f) $H_2C{=}C{=}CH_2$; (g) $CH_3—CCl_3$

12. How many signals would you expect to find in the ^1H·NMR spectrum of each of the following compounds?

(a) 1-Bromobutane, (b) butane, (c) 1,4-dibromobutane (d) 2,2-dibromobutane, (e) 2,3,3,3-tetrabromobutane, (f) 1,1,4-tribromobutane.

Solution

(a) **1-Bromobutane ($\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}H_2Br$)**

The protons attached to C-1, C-2, C-3 and C-4 are chemical shift nonequivalent. Therefore, 4 signals are expected to be found in the NMR spectrum of 1-bromobutane.

(b) **Butane ($\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}H_3$)**

Protons at C-1 are chemical-shift equivalent to the protons at C-4. Similarly, the protons at C-2 are chemical shift equivalent to the protons at C-3. However, the six protons at C-1 and C-4 are chemical-shift nonequivalent to the four protons at C-2 and C-3. Therefore, two signals are expected to be found in the NMR spectrum of butane.

(c) **1,4-Dibromobutane ($Br\overset{1}{C}H_2\overset{2}{C}H_2\overset{3}{C}H_2\overset{4}{C}H_2Br$)**

The spectrum is similar to butane.

(d) **2,2-Dibromobutane ($\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}Br_2\overset{1}{C}H_3$)**

The protons at C-1, C-3 and C-4 are not chemical-shift equivalent. Therefore, three signals are expected to be found in the NMR spectrum of 2,2-dibromobutane.

(e) **2,2,3,3-Tetrabromobutane ($\overset{1}{C}H_3\overset{2}{C}Br_2\overset{3}{C}Br_2\overset{1}{C}H_3$)**

The protons at C-1 and C-4 are chemical-shift equivalent. Therefore, only one signal is expected to be found in the NMR spectrum of this compound.

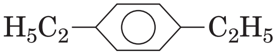
(f) **1,1,4-Tribromobutane ($Br\overset{4}{C}H_2\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}HBr_2$)**

Protons at C-1, C-2, C-3 and C-4 are chemical-shift nonequivalent. Therefore, four signals are expected to be found in the NMR spectrum of this compound.

13. Describe the appearance of the ^1H NMR spectrum of each of the following compounds. How many signals would you expect to find, and into how many peaks will each signal be split?

(a) $\mathbf{ClCH_2OCH_2CH_3}$ **(b)** $\mathbf{CH_3CH_2OCH_3}$

(c) $\mathbf{CH_3CH_2OCH_2CH_3}$ **(d)**

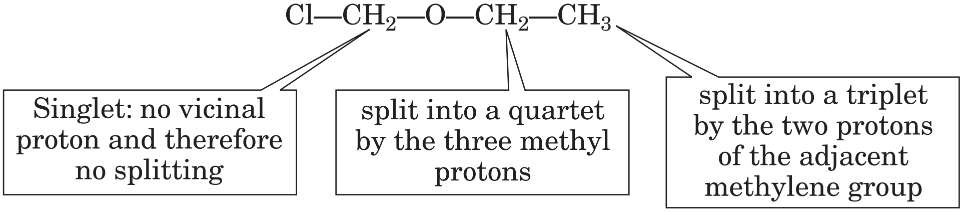


H_5C_2—C₆H₄—C_2H_5

Solution

(a) $ClCH_2O\overset{1}{C}H_2\overset{2}{C}H_3$

The protons at C-1, C-2 and of the chloromethyl group (—CH_2Cl) are chemical-shift nonequivalent. Therefore, three signals are expected to be found in the NMR spectrum of this ether. The splitting pattern of the signals may be depicted as follows:



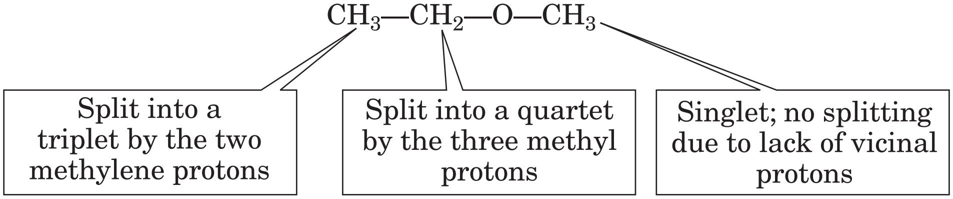
$Cl—CH_2—O—CH_2—CH_3$

Singlet: no vicinal proton and therefore no splitting

split into a quartet by the three methyl protons

split into a triplet by the two protons of the adjacent methylene group

(b) There signals, one each for the two methyl protons and one for the methylene protons, are expected to be found in the spectrum of this compound. The splitting pattern of the signals may be depicted as follows:



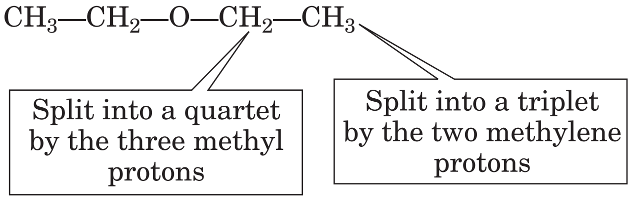
$CH_3—CH_2—O—CH_3$

Split into a triplet by the two methylene protons

Split into a quartet by the three methyl protons

Singlet; no splitting due to lack of vicinal protons

(c) Since the six methyl protons are chemical-shift equivalent and the four methylene protons are also chemical-shift equivalent, two signals are expected to be found in the NMR spectrum of this ether. The splitting pattern of the signals may be depicted as follows:

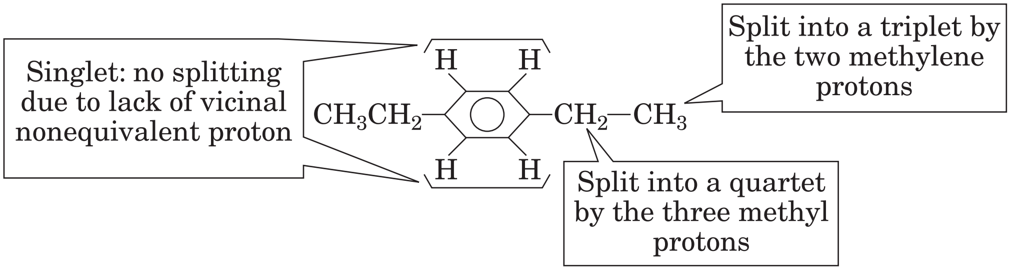


$CH_3—CH_2—O—CH_2—CH_3$

Split into a quartet by the three methyl protons

Split into a triplet by the two methylene protons

(d) Three signals, one for the six equivalent methyl protons, one for the four equivalent methylene protons and one for the four equivalent ring protons, are expected to be found in the spectrum of *p*-diethylbenzene. The splitting pattern of the signals may be depicted as follows:



Singlet: no splitting due to lack of vicinal nonequivalent proton

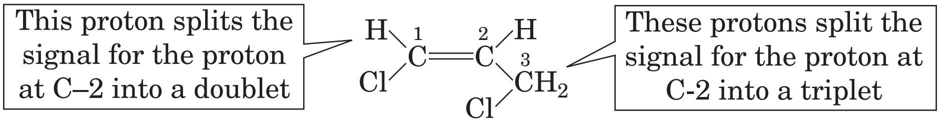
Split into a triplet by the two methylene protons

Split into a quartet by the three methyl protons

14. Describe the splitting pattern expected for the protons at (a) C-2 in (Z)-1,3-dichloropropene and (b) C-2 in 2-bromopropanal.

Solution

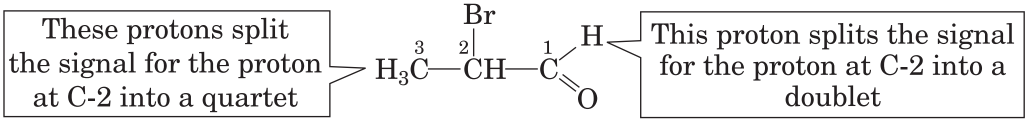
(a) The signal of the proton at C-2 is split into a doublet by coupling with the proton *cis* to it on the double bond and each line of this doublet is split into a triplet by the two protons of the —CH_2Cl group, i.e., the signal appears as a triplet of doublets (a set of six peaks), i.e., a multiplet.



This proton splits the signal for the proton at C–2 into a doublet

These protons split the signal for the proton at C-2 into a triplet

(b) The signal of the proton at C-2 is split into a quartet by the three methyl protons and each line of this quartet is split into a doublet by the —CHO proton; the result is a eight-line signal or multiplet.



These protons split the signal for the proton at C-2 into a quartet

This proton splits the signal for the proton at C-2 into a doublet

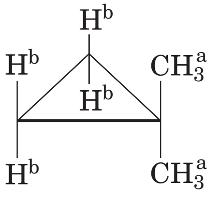
15. Predict the number of signals in (a) 1,1,-dimethylcyclopropane, (b) *trans*-1,2-dimethylcyclopropane and (c) *cis*-1,2-dimethyl-cyclopropane.

Solution

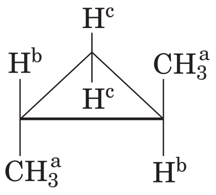
(a) Two signals, one for the six equivalent methyl protons (H^a), and one for the four equivalent ring protons (H^b), are expected to be found in the NMR spectrum of 1,1-dimethylcyclopropane.

(b) Three signals, one for the six equivalent methyl protons (H^a), one for the two equivalent protons (H^b) attached to the carbons bearing methyl and one for the two equivalent CH_2 protons (H^c) are expected to be found in the NMR spectrum of *trans*-1,2-dimethylcyclopropane. In fact, the CH_2 protons (H^c) are each *cis* to a CH_3 and *trans* to a CH_3.

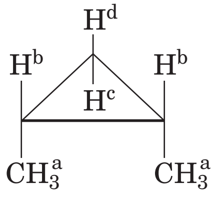
(c) In *cis*-1,2-dimethylcyclopropane, the two CH_2 protons (H^c and H^d) are different (diastereotopic) since H^c is *cis* to the methyls and H^d is *trans* to methyls. Therefore, four signals, one for the six equivalent methyl protons (H^a), one for the two equivalent protons (H^b) attached to the carbons bearing methyl, one for the H^c proton and one for the H^d proton, are expected to be found in its NMR spectrum.



1,1-Dimethylcyclopropane (*two signals)*



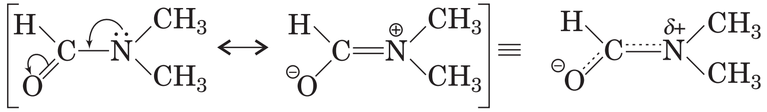
trans-1,2-Dimethylcyclopropane (*three signals)*

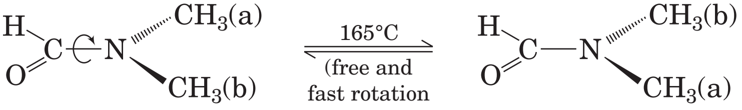


cis-1,2-Dimethylcyclopropane (*four signals*)

16. The NMR spectrum of dimethylformamide, $HCON(CH_3)_2$, shows two signals for the methyl groups at room temperature but only one signal at 165°C. Explain.

Solution In dimethylformamide, the C—N bond acquires some double bond character due to resonance and this imposes some restriction on free rotation of the two methyl groups around the C—N bond.



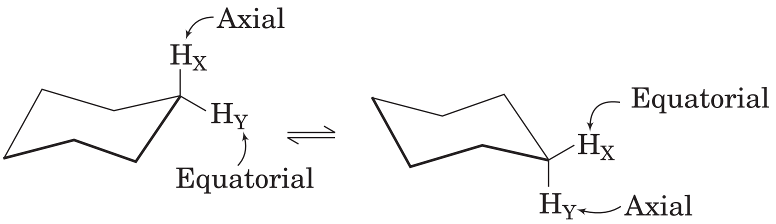


At low temperature, i.e., at room temperature, the rotation of the —NMe_2 group around the C—N bond is slow and under such conditions the NMR senses one methyl group *cis* and one methyl group *trans* to the aldehydic hydrogen atom, i.e., the two methyl groups become nonequivalent (diastereotopic in nature) and for this, two signals are obtained for the two methyl groups. However, at 165°C, the rate of rotation of the —NMe_2 group around the C—N bond is relatively fast. The two methyl groups then become equivalent and the instrument then sees only the average environment of all the six protons. The result is the formation of only one signal for the two methyl groups.

17. (a) Explain why cyclohexane has single sharp signal although it has conformationally different hydrogens. (b) Under what conditions might more than a single signal be observed for this compound?

Solution

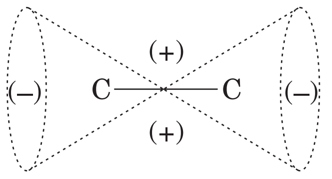
(b) The equatorial and axial hydrogens of cyclohexane should each give different signals. However, the two chair conformers are interconverted so rapidly that NMR sees the average environment of all the protons and as a result, a single signal is obtained that has a chemical shift midway between the true chemical shift of the axial and the equatorial protons.



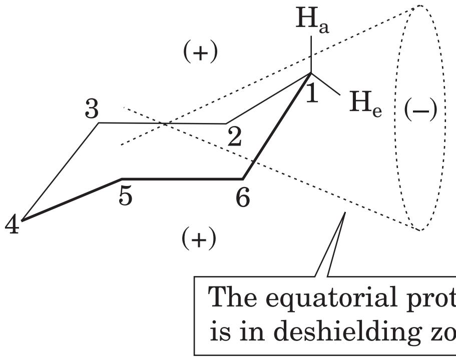
(b) At sufficiently low temperatures, the interconversion of conformers becomes very slow, and in that case, signals for each conformationally different hydrogens are obtained. The intensities of these individual signals would correspond to the actual population of the conformer at the temperature attained.

18. Explain why in a rigid cyclohexane system an equatorial proton is always found downfield (by about δ 0.5) than the axial proton on the same carbon.

Solution In contrast with the striking anisotropic effects of circulating π-electrons, the σ electrons of a C—C bond produce a relatively small effect. The axis of the C—C bond in cyclohexane, for example, is the axis of the deshielding cone. The axial and equatorial protons on a carbon, e.g., C-1, are oriented similarly with respect to C-1—C-2 and C-1—C-6 bonds, but the equatorial proton is within the deshielding cone (zone) of the C-2—C-3 bond (and C-5—C-6 bond). It is for this reason an equatorial proton in cyclohexane is always found a little downfield (~δ 0.5) than the axial proton on the same carbon.



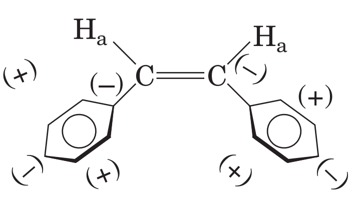
Shielding zone ⇒ (+)
Deshielding zone ⇒ (–)



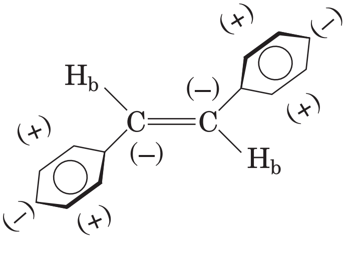
The equatorial proton is in deshielding zone

19. By NMR spectral analysis how would you distinguish between *cis*- and *trans*-stilbene?

Solution



cis-Stilbene
$\delta(H_a) = 6.99$ ppm

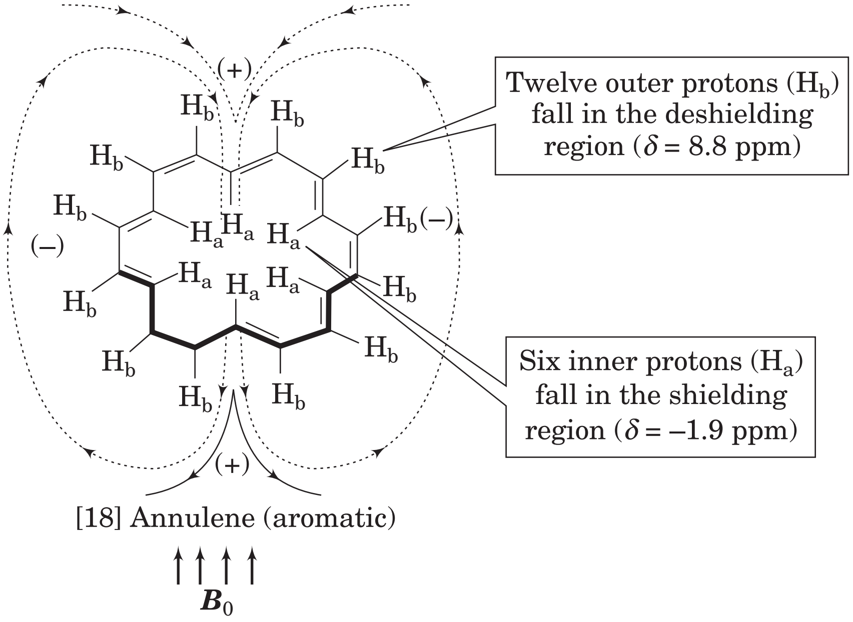


trans-Stilbene
$\delta(H_b) = 6.49$ ppm

In *trans*-stilbene, both the chemically equivalent ethylenic protons (H_b) are deshielded by both the benzene rings because both of them fall in the deshielding zone of each ring. However, in the *cis*-isomer, each of these protons (H_a) is deshielded by only one adjacent ring. Because of this, in *trans*-stilbene, the protons (H_b) appear at somewhat downfield as compared to the protons (H_a) of *cis*-stilbene. Therefore, these two isomeric stilbenes can be distinguished by comparing the chemical shift values of the ethylenic protons.

20. Explain why the six inside protons of [18] annulene give NMR signal at much upfield (δ = 1.9 ppm), whereas the twelve outside protons give signal at much downfield (δ = 8.8 ppm).

Solution [18] Annulene is an aromatic compound [a $(4n + 2)\pi$ system, where $n = 4$] and produces ring current in the presence of external magnetic field causing anisotropic effect. The protons on the outside of the ring fall in the deshielding region and appear at much downfield (δ = 8.8 ppm). On the other hand, the protons inside the ring fall in the shielding region and appear at much upfield (δ = –1.9 ppm, i.e., at a field higher than TMS).



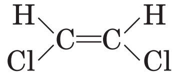
Twelve outer protons (H_b) fall in the deshielding region (δ = 8.8 ppm)

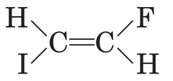
Six inner protons (H_a) fall in the shielding region (δ = –1.9 ppm)

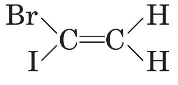
[18] Annulene (aromatic)

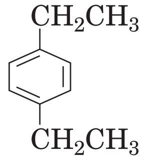
21. In which of the following molecules does spin-spin coupling occur? Give the multiplicity of each kind of protons when splitting is observed.

(a) $BrCH_2CH_2Br$ **(b)** $BrCH_2CH_2Cl$ **(c)** $(CH_3)_3CCH_2Cl$

(d)


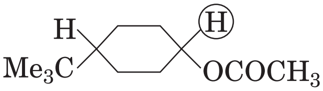
(e)


(f)


(g)


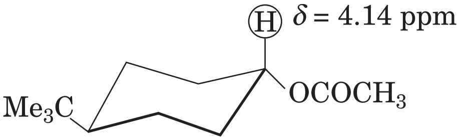
Solution Splitting does not take place in (a) or (d) because each one has only equivalent protons. Also, there is no splitting in (c) because it has no nonequivalent protons on adjacent carbons. The protons of CH_2 in (b) are nonequivalent and each is split into a triplet ($n = 2$; $2 + 1 = 3$). The two protons in (e) are non-equivalent and each is split into a doublet. The vinylic protons in (f) are nonequivalent because one is *cis* to Br and other is *cis* to I (actually they are diastereotopic). Each is split into a doublet. The compound (g) gives a singlet for the four equivalent uncoupled ring protons, a quartet for the two equivalent CH_2 protons, coupled with CH_3, and a triplet for the two equivalent CH_3 protons coupled with CH_2.

22. Predict the chemical shifts of axial and equatorial hydrogens in substituted cyclohexanes from the following observations:

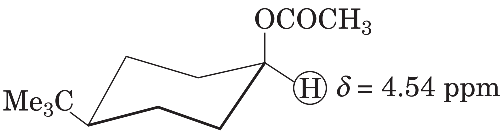


δ for the encircled H in *trans*-isomer = 4.14 ppm
and δ for the encircled H in *cis*-isomer = 4.54 ppm

Solution The bulky *tert*-butyl group practically freezes the compound in that particular conformation in which it occupies the equatorial position. Therefore, in the *trans*-1,4-isomer, the substituents are both equatorial and consequently, the encircled hydrogen is axial. In the *cis*-1,4-isomer the bulky *tert*-butyl group is equatorial, the —$OCOCH_3$ group is axial and so, the encircled hydrogen is equatorial.



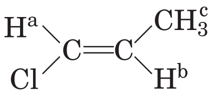
trans



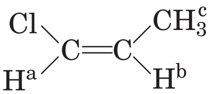
cis

Hence, an equatorial hydrogen appears at more downfield than its axial counterpart.

23. How would you distinguish between the following geometric isomers I and II using ^{1}H NMR spectroscopy?



I (*trans*)



II (*cis*)

Solution For each of these two geometric isomers, the chemical shifts, relative intensities, and coupling patterns are the same. They differ only in J_{ab} value; it is much larger in I (the *trans* isomer) than in II (the *cis* isomer). Therefore, the two geometric isomers can be differentiated by their coupling constant values.

24. Compare the NMR spectra of CH_3CH_2Cl and CH_3CHDCl.

Solution Deuterium does not resonate (give signals) under the conditions used for H. Also, its coupling with an H is so weak that it merely broadens the H signal without splitting it (splitting, however, observed at very high resolution). Therefore, CH_3CHDCl has a doublet for the methyl hydrogens and typical downfield quartet for the single hydrogen. In CH_3CH_2Cl, the methyl hydrogens appear as a triplet and the methylene hydrogens appear as a quartet.

25. How would you verify that a particular signal arises from an H of the following groups: —OH, —NH, —SH?

Solution The spectrum of the compound is first recorded. Then excess of D_2O is added to the sample solution and the spectrum is recorded once again. The hydrogens in these groups are replaced by deuterium. For example:

$$\text{R—O—H} + D_2O \rightleftharpoons \text{R—O—D} + \text{DOH}$$

Since deuterium does not resonate under the conditions used for hydrogen, the original peak for the —OH proton practically disappears in the spectrum rerun in D_2O. A new signal for DOH appears.

26. Comment on the splitting of (a) H and (b) F for 2,2-difluoropropane.

Solution

(a) Fluorine, like hydrogen, has half-spin (+1/2 and –1/2) nuclei and therefore, it splits the peak of a vicinal hydrogen according to the $n + 1$ rule. In $CH_3CF_2CH_3$, the two fluorine atoms split the six equivalent methyl hydrogens into a 1:2:1 triplet.

(b) The NMR spectrum of the NMR active fluorine can be obtained with the aid of a special probe using a different frequency than used for hydrogen. The six adjacent methyl hydrogens split the signal produced by F into a septet.

27. Methanol shows two singlets in carbon tetrachloride but a doublet and a quartet in DMSO-d_6. Explain these observations.

Solution Hydrogens involved in intra- or intermolecular H-bonding move back and forth from one OH to another so rapidly that they cannot couple with vicinal hydrogens. Because of intermolecular H-bonding, this situation occurs in carbon tetrachloride and as a consequence, coupling does not take place. Each kind of hydrogen appears as a singlet. However, in DMSO-d_6 $[(CD_3)_2S{=}O]$, H-bonding occurs with the solvent and the hydrogen stays on the oxygen of OH. Because of this, the typical coupling pattern (3-H doublet and 1-H quartet) is observed.

28. What do you mean by magnetically non-equivalent protons?

Solution Chemically equivalent protons having different coupling constant to every other nucleus in the molecule are known as magnetically non-equivalent protons.

29. Aldehydic proton (—CHO) appears much downfield in the PMR spectrum—why?

Solution The aldehydic proton is strongly deshielded (δ 9-10 ppm) because it lies in the deshielding zone of the C═O group.

30. Assign the structure for each of the following compounds from the given proton NMR spectral data. Values of δ are in ppm and *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, etc.

- **(a) M.F.: $C_3H_5Cl_3$; proton NMR: δ 2.20(3H, s); 4.02(2H, s).**
- **(b) M.F.: C_3H_7ClO; proton NMR: δ 2.0(2H, p); 2.8 (1H, s); 3.7(2H, t); 3.8 (2H, t)**
- **(c) M.F.: $C_{10}H_{14}$; proton NMR: δ 1.30(9H, s); 7.30(5H, s)**
- **(d) M.F.: C_4H_8O; proton NMR: δ 1.07(3H, t); 2.12(3H, s); 2.50(2H, q).**
- **(e) M.F.: C_3H_7Br; proton NMR: δ 1.75 (6H, d); 4.30(1H, s).**
- **(f) M.F.: C_7H_9ON; proton NMR: δ 3.75(3H, s); 5.85(2H, s, broad); 6.35 (2H, d, *J* = 9.0 Hz); 6.52 (2H, d, *J* = 9.0 Hz)**
- **(g) M.F.: C_6H_{12}; proton NMR: δ 0.9 (3H, t); 1.6(3H, s); 1.7(3H, s); 2.0(2H, p); 5.1(1H, t).**

Solution

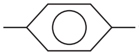
(a) The 3-H singlet arises from a CH_3 group with no vicinal hydrogen and 2-H singlet arises from a CH_2 group with no vicinal hydrogen. Each of them has only two vicinal chlorines. Therefore, the structure of the compound is $CH_3CCl_2CH_2Cl$. Due to the —I effect of the terminal Cl atom, the CH_2 protons appear at somewhat downfield (δ 4.02) compared to the CH_3 protons (δ 2.20).

(b) The 1-H singlet at δ 2.8 indicates the OH proton. There are three CH_2 groups. The middle one shows a pentet (n = 4) because the two different flanking CH_2 groups have similar coupling constant (J) values. Therefore, the structure of the compound is $ClCH_2CH_2CH_2OH$.

(c) The appearance of a 5-H singlet in the aromatic region suggests that the compound is a monosubstituted benzene. The 9-H singlet indicates the presence of three methyls with no vicinal hydrogen, i.e., a *tert*-butyl group. Therefore, the structure of the compound is $C_6H_5C(CH_3)_3$.

(d) Since the compound is an aliphatic one, the 2-H singlet at δ 2.12 indicates the presence of three acetyl protons (CH_3CO—). A 3-H triplet at δ 1.07 and a 2-H quartet at δ 2.50 indicates the presence of an ethyl (—CH_2CH_3) group. Hence, the structure of the compound is $CH_3COCH_2CH_3$.

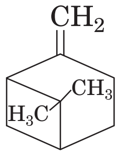
(e) The 6-H doublet at δ 1.75 is due to six equivalent protons of two methyl groups which are coupled with one methaine proton ($C\mathbf{H}_3$—CH—$C\mathbf{H}_3$). The 1-H septet (multiplet) at δ 4.30 is due to the lone methine proton which is coupled with six protons of the two adjacent methyl groups. Hence, the structure of the compound is $CH_3CHBrCH_3$.

(f) The 3-H singlet at δ 3.75 is due to three equivalent methyl protons. The chemical shift is quite characteristic of a methoxy (—OCH_3) group. The 2-H broad singlet at δ 5.85 is due to the presence of an —NH_2 group. The 2-H *o*-coupled doublet at δ 6.35 (*J* = 9.0 Hz) is due to the ring protons *ortho* to the —NH_2 group. The other 2-H o-coupled doublet at δ 6.52 (*J* = 9.0 Hz) is due to two ring protons *ortho* to the —OCH_3 group. Therefore, the structure of the compound is 

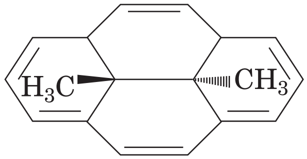
(g) The 1-H triplet at δ = 5.1 indicates the presence of a vinylic proton which is split by a vicinal CH_2 group. The 3-H triplet at δ 0.9 indicates the presence of a CH_3— group (a part of CH_3CH_2—group) and the 2-H pentet (instead of an octet) at δ 2.0 is due to two —CH_2— protons. One 3-H singlet at δ 1.7 and the other 3-H singlet at δ 1.6 are due to the $=C(CH_3)_2$ group. One CH_3 is *cis* to the vinylic hydrogen and the other is *trans* to the vinylic hydrogen (diastereotopic). Therefore, the structure of the compound is $CH_3CH_2CH{=}C(CH_3)_2$.

31. Explain the following observations:

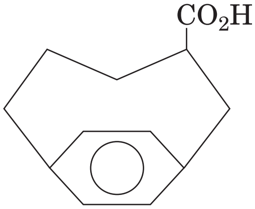
- **(a) The two methyl groups of the bridge isopropyl group in β-pinene (I) absorb differently.**
- **(b) The methyl groups of 15,16-dihydro-15,16-dimethylpyrene (II) are found to absorb at δ –4.23.**
- **(c) In the following cyclophane compound (III) one of the two protons of the central CH_2 group appears at δ –1.4.**
- **(d) The bridge protons of 1,6-methano[10]annulene(IV) appears at δ –0.5.**



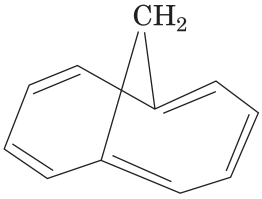
I



II



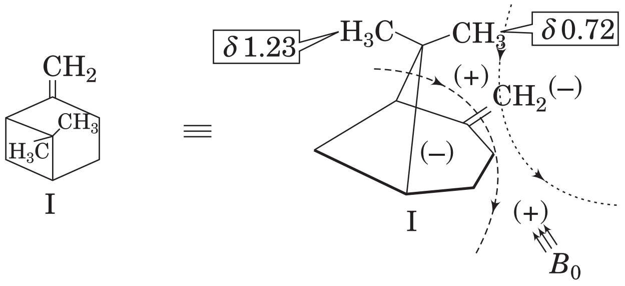
III



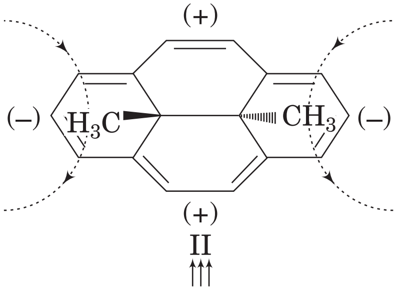
IV

Solution

(a) Any group held above or below the plane of the double bond will experience a shielding effect, since in these areas the induced field opposes B_0. In β-pinene (I), one of the geminal methyl groups is held in just such a shielded position, and as a consequence, it comes to resonance at significantly lower δ than its twin.

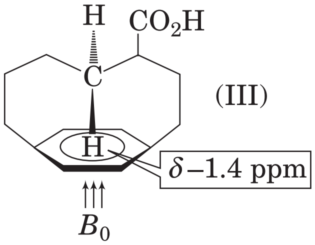


(b) The compound II is aromatic [a(4*n* + 2)π electron system, where *n* = 3]. The cyclic π electron system around the periphery of the molecule sustains a substantial ring current. The two methyl groups are deep in the shielding zone of this ring current, and it is for this reason that they appear at such an abnormally low δ value (–4.23).



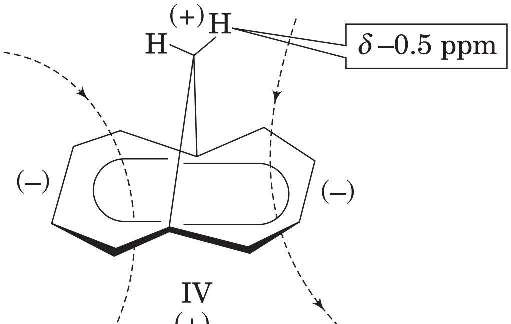
II

(c) In this compound (III), one of the methylene protons is found to be placed in the centre of the ring, i.e., within the circulating zone. Because of this, it becomes considerably shielded (appears at δ –1.4).



(III)

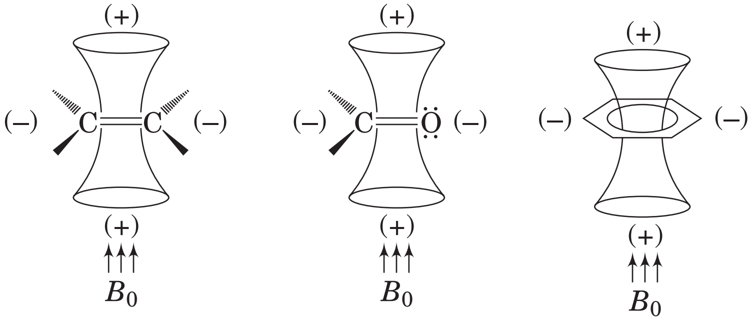
(d) In compound IV, the bridge protons are found to be placed in the centre of the ring, i.e., within the circulating zone. For this reason, it becomes considerably shielded (δ –0.5).

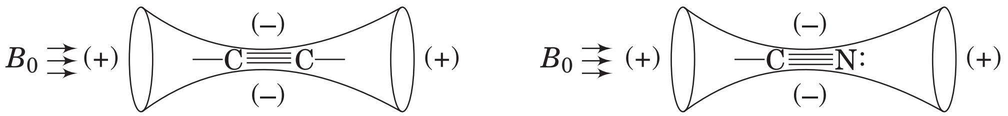


IV

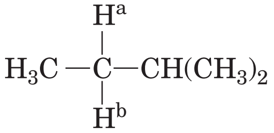
32. Show with diagram how a double bond, a triple bond or a benzene ring can produce shielding and deshielding regions around them in the presence of external magnetic field.

Solution The shielding and deshielding regions [(+) and (–)] around a double bond, a triple bond or a benzene ring may be shown as follows:

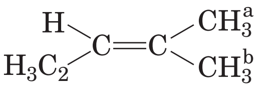


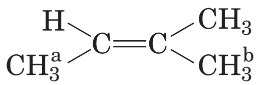


33. Specify whether the labelled protons in each of the following hydrocarbons are expected to have the same or different chemical shift.

(a) 

$$H_3C-\overset{H^a}{\underset{H^b}{C}}-CH(CH_3)_2$$

(b) 

(c) 

Solution

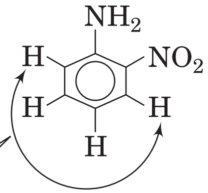
(a) The two marked protons in this compound (H^a and H^b) are enatiotropic, and therefore, they are chemically equivalent. Hence, they are expected to have the same chemical shift value in its NMR spectrum.

(b) The marked CH_3 groups are diastereotropic, and, therefore, chemically nonequivalent. Consequently, the protons belonging to these groups have different chemical shift.

(c) The marked methyl groups are chemically different in the sense that they are attached to different carbon atoms of the C=C system. Therefore, they are chemically different and would exhibit different chemical shift.

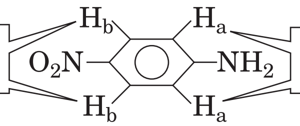
34. How would you distinguish between *o*- and *p*-nitroaniline by proton NMR?

Solution The *ortho*-isomer of nitroaniline has four chemically nonidentical protons but all of them are aromatic hydrogens. Each of them will split into doublets but they will appear as a complex multiplet at around δ 7.6. On the other hand, the *para*-isomer has two pairs of chemically distinguishable hydrogens. Each of them will appear as 2H doublet. H^a proton will appear at δ 7.4 (slightly upfield) and H^b protons will appear at δ 8.1 (slightly downfield). Therefore, two isomeric nitroanilines can be well distinguished from their ^1H NMR signals of aromatic hydrogens.



Appears as multiplet at around δ 7.6

o-Nitroaniline



Appears as doublet at δ 8.1

Appears as doublet at δ 7.4

p-Nitroaniline

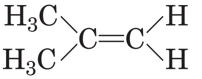
35. Predict the number of signals produced by each of the following compounds:

(a) $CH_3CH_2OCH_3$

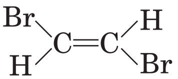
(b) $CH_3CHBrCH_3$

(c) $(CH_3)_3COCH_3$

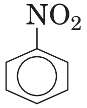
(d)



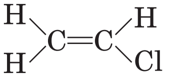
(e)



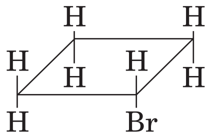
(f)



(g)

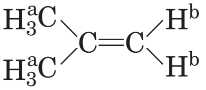


(h)



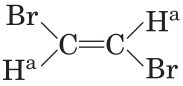
Solution (a) $CH_3^aCH_2^bOCH_3^c$ (three signals); (b) $CH_3^aCH^bBrCH_3^a$ (two signals);

(c) $(CH_3^a)_3COCH_3^b$ (two signals); (d)

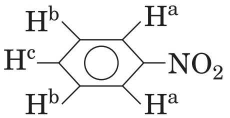


(two signals);

(e)

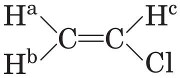


(one signal); (f)

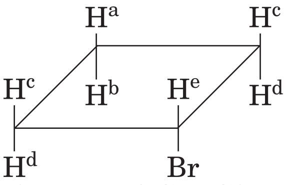


(three signals);

(g)



(three signals) and (h)



(five signals)

36. The ^1H NMR spectrum of a mixture of CH_3Cl and $(CH_3)_3CBr$ shows two singlets of δ 3.05 and δ 1.8 respectively with relative integrals of 5:1. What is the mole per cent of each compound in the mixture?

Solution From the relative integrals we may write:

$$\frac{5 \text{ protons of } CH_3Cl \times \frac{1}{3} \text{ molecule per proton}}{1 \text{ proton of } (CH_3)_3\ CBr \times \frac{1}{9} \text{ molecule per proton}} = \frac{15 \text{ molecules of } CH_3Cl}{1 \text{ molecule of } (CH_3)_3CBr}$$

$$\therefore \quad \text{Mole fraction of } CH_3Cl = \frac{15}{15+1} = \frac{15}{16} = 0.938$$

Hence, the sample contains 93.8% CH_3Cl and 6.2% $(CH_3)_3CBr$.

37. (a) What is the relationship between the chemical shift in ppm and the operating frequency of the instrument?

(b) What is the relationship between the chemical shift in hertz (Hz) and the operating frequency?

(c) What is the relationship between the coupling constant (*J*) and the operating frequency?

Solution

(a) The chemical shift in ppm is independent of the operating frequency.

(b) The chemical shift in hertz (Hz) is proportional to the operating frequency.

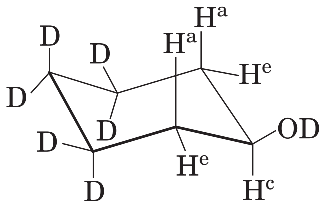
(c) The coupling constant (*J*) is independent of the operating frequency.

38. Predict the relative intensities of the peaks in a quintet using a diagram that shows the ways in which the magnetic fields of four protons can be aligned.

Solution A quintet can be obtained by coupling to four equivalent protons on adjacent carbons. The four protons can be aligned in five different ways. The following possible arrangements for the alignment of four protons suggest that the relative intensities of a quintet are 1:4:6:4:1.

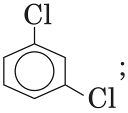
↑↑↑↑	↑↑↑↓	↑↑↓↓	↑↓↓↓	↓↓↓↓
	↑↑↓↑	↓↓↑↑	↓↑↓↓	
	↑↓↑↑	↑↓↑↓	↓↓↑↓	
	↓↑↑↑	↓↑↓↑	↓↓↓↑	
		↑↓↓↑		
		↓↑↑↓		

39. Comment on the ^{1}H NMR spectrum of the following compound and explain why a 100 MHz instrument instead of a 60 MHz instrument is used for this study.



Solution H^a and H^e are diastereotopic and because of this, they couple with each other as well as with H^c. Hence, H^a and H^e both appear as two pairs of doublets, the axial H being more upfield. The most downfield proton H^e (as it is attached to a carbon containing oxygen) is split into a triplet by the two H^a protons and each signal of this triplet is further split into a triplet by two H^e protons. When a 60 MHz instrument is used, the two inner peaks of the H^a doublets are so close that they merge into a broad peak which appears like a triplet. A 100 MHz instrument is used to get well separated doublets.

40. How can you distinguish the following molecules by ^{1}H-NMR spectroscopy?



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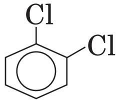


[**Hint:** *m*-Dichlorobenzene gives three NMR signals, whereas *o*-dichlorobenzene gives two NMR signals.]

41. How can you distinguish between the following pairs by ^{1}HNMR?

(a) $CH_3CH_2C{\equiv}CH$ and $H_3C{-}C{\equiv}C{-}CH_3$

(b) Phenyl acetate (CH_3COOPh) and methyl benzoate (PhCOOMe)

[CU 2017]

[**Hint:** (a) The terminal alkyne (but-1-yne) produces three NMR signals, whereas the nonterminal alkyne (but-2-yne) produces only one NMR signal.

(b) In methyl benzoate the 3H singlet (due to CH_3) appears at somewhat downfield compared to that in phenyl acetate and this is because in the former the —CH_3 group is directly attached to electronegative oxygen atom.]

42. A compound ($C_4H_6O_2$) shows a very strong IR bond at 1,720 cm^{-1} and only one singlet signal in its ^{1}H NMR spectrum. Analyse the structure of the compound. [CU 2011]

[**Hint:** $CH_3COCOCH_3$]

43. Why TMS is used as the reference compound in scanning ^{1}H-NMR spectrum of a compound? [CU 2011]

[**Hint:** See ***Solved Question No. 8.***]

44. Sketch the ^{1}H-NMR spectrum with integrations showing relative chemical shifts of *m*-dinitrobenzene. [CU 2013]

[**Hint:** δ 9.08 (1H, s), 8.61 (2H, m), 7.87 (1H, m) respectively for protons *ortho* to both $-NO_2$, *para* to both $-NO_2$, and *meta* to both $-NO_2$ groups.]

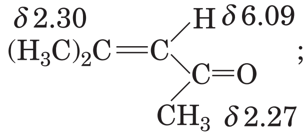
45. Aromatic protons are more deshielded than ethylenic protons, although both types of protons are attached to *sp*^{2}-hybridized carbon atoms—Explain. Why TMS is used as reference compound for ^{1}H NMR?

[CU 2013]

[**Hint:** The secondary magnetic field generated by circulating π-electrons (ring current) deshields aromatic protons much effectively because it is relatively stronger than that generated in an alkene.]

46. A compound having molecular formula $C_6H_{10}O$ shows a 6H singlet at 230 ppm, a 1H singlet at 6.09 ppm and a 3H singlet at 2.27 ppm in the NMR spectrum. The compound shows UV absorption at λ_{max} 230 nm and 329 nm in hexane. Identify the structure of the compound with proper assignment of the NMR signals. [CU 2014]

[**Hint:**



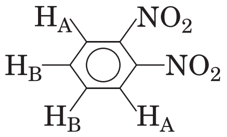
; it can exist in two conformations (*s-cis* and *s-trans*)]

47. Sketch the ^{1}H-NMR spectrum with integrations showing relative chemical shifts of isomeric dibromoethanes. [CU 2014]

[**Hint:** $BrCH_2CH_2Br$: δ 3.65 (2H, s); CH_3CHBr_2 : δ 2.45 (3H, d) and δ 5.84 (1H, q)]

48. How many signals will you expect in ^{1}H-NMR spectrum of *o*-dinitrobenzene? Assign the signals and arrange them in the increasing order of their chemical shifts. State the splitting pattern of the signals. [CU 2015]

[**Hint:** *o*-Dinitrobenzene is, in fact, a AA′BB′ system because the hydrogens *ortho* to one $-NO_2$ and *meta* to other and the hydrogens *para* to one $-NO_2$ and *meta* to other are chemically equivalent but magnetically non-equivalent. These magnetic non-equivalences can lead to some extremely complex ^{1}H-NMR spectrum of *o*-dinitrobenzene. If the system is considered as an AB system by ignoring magnetic nonequivalence, two doublets (one for A protons and the other for B protons) are expected. In fact, at lower resolution two doublets are obtained. The two A protons appear at somewhat downfield compared to B protons.



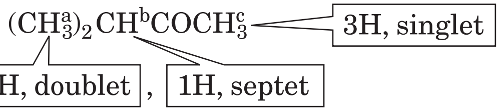
$\delta_{H_A} > \delta_{H_B}$

49. Write the structure of the compound $C_5H_{11}Cl$ which shows two singlets in its ^{1}H-NMR spectrum. [CU 2016]

[**Hint:** $(CH_3)_3CCH_2Cl$: (9H, s) and (2H, s)]

50. Predict the relative chemical shifts, multiplicities and relative intensities of the ^{1}H-NMR spectrum of $(CH_3)_2CHCOCH_3$. [CU 2016]

[**Hint:**

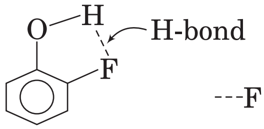


$$\underbrace{(CH^a_3)_2}_{\boxed{\text{6H, doublet}}}\underbrace{CH^b}_{\boxed{\text{1H, septet}}}CO\underbrace{CH^c_3}_{\boxed{\text{3H, singlet}}}$$

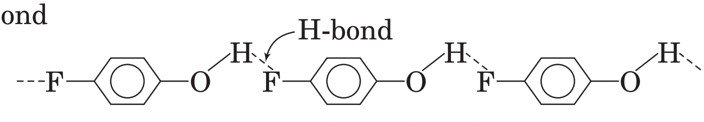
δ : $H^c > H^b > H^a$]

51. How would you distinguish between *o*- and *p*-fluorophenol by ^{1}H-NMR spectroscopy?

[**Hint:**



o-Fluorophenol
(due to intramolecular
H-bonding, the signal position
of OH proton does not change
with change in concentration)



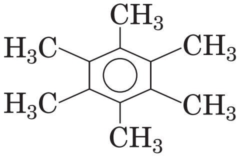
p-Fluorophenol
(due to intermolecular
H-bonding, the signal position
of OH proton changes
with change in concentration)

52. Define the term chemical shift. What difference in chemical shift values are expected for the protons of CH_3F, CH_3Cl and CH_3Br?

[**Hint:** See article no. 4.4.5. The chemical shift of methyl halides depends on the electronegativity of the corresponding halogen atom. Deshielding increases with increase in electronegativity of halogen and as consequence, the methyl protons appears progressively at more downfield.

CH_3F (electronegativity of F = 4.0) : δ 4.26; CH_3Cl (Cl = 3.1); δ 3.05;
CH_3Br(Br = 2.8) : δ 2.68]

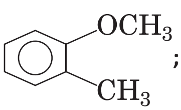
53. A compound having molecular formula $C_{12}H_{18}$ is characterized by ^{1}H-NMR spectrum which contains a single peak at δ 2.2 as singlet. Identify the compound. [CU 2018]

[**Hint:**  (Hexamethylbenzene)

All the protons are chemical-shift equivalent, and therefore, a sigle peak at δ 2.2 is obtained as singlet.]

54. Which of the compounds below most closely matches the following ^{1}H-NMR data? [CU 2018]

δ value	No. of protons	Splitting
7.6	2H	Doublet
7.3	2H	Doublet
3.5	3H	Singlet
2.2	3H	Singlet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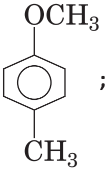
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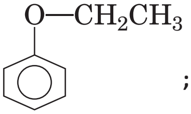
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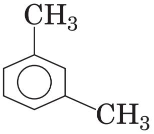
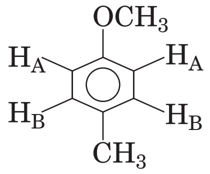


[**Hint:**

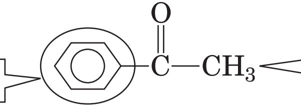


4-Methylanisole

—OCH_3 : δ 3.5 (3H, s)
—CH_3 : δ 2.2 (3H, s)
H_A : δ 7.3 (2H, d)
H_B : δ 7.6 (2H, d)]

55. A compound C_8H_8O gives the following spectra:
IR : 3,100, 1,700(s), 1,640, 1,680 cm^{-1}
^{1}H-NMR: δ 7.3–8.2 (complex multiplet), δ 2.5 (3H, s)
Identify the compound with proper justification. **[CU 2018]**

[**Hint:**



5H, m, δ 7.3–8.2

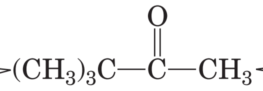
3H, s, δ 2.5

(C_8H_8O)

C=O stretching (conjugated with phenyl): 1,680 –1,700 cm^{-1};
C—H stretching: 3100 cm^{-1}]

56. A compound having molecular formula $C_6H_{12}O$ shows in its ^{1}H-NMR spectrum two signals at δ 1.1 (ppm), 9H and 2.1 (ppm), 3H, both as singlets. Identify the compound. **[CU 2018]**

[**Hint:** 9H, s, δ 1.1

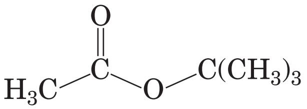


$$(CH_3)_3C-\overset{\overset{O}{\|}}{C}-CH_3$$

3H, s, δ 2.1]

($C_6H_{12}O$)

57. The structural formulas for two isomeric esters (M.F. $C_6H_{12}O_2$) are as follows:



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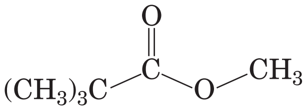
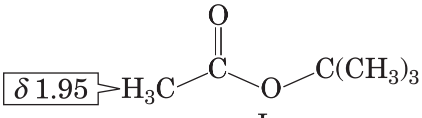


II

(a) Predict the number of signals in the ^{1}H-NMR spectrum of each ester.
(b) Predict the ratio of areas of the signals in each of these spectrums.
(c) How would you distinguish between these two isomers on the basis of chemical shift?

Solution

(a) The ^{1}H-NMR spectrum of each ester consists of two signals.
(b) In each spectrum, the signals are obtained in the ratio 9:3 or 3:1.
(c) The two isomers can be distinguished by the chemical shift value of the single –CH_3 group. The hydrogen of –OCH_3 are more deshielded (appear farther downfield) than the hydrogen of –$COCH_3$.



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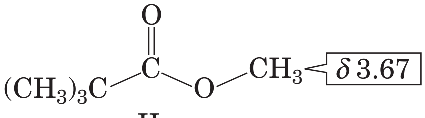
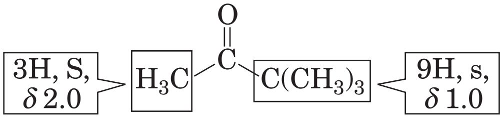


II

Conjoint IR-UV-NMR Spectrometry Problems

58. An organic compound ($C_6H_{12}O$) showed two signals in its ^{1}H-NMR spectrum at δ 1.0 (9H, s) and δ 2.0 (3H, s). An intense IR band of this compound appears at 1715 cm^{-1}. However, there is no absorption in the range 2,700–2,860 cm^{-1}. Determine the structure of the compound.

Solution The molecule showed IR absorption band at 1,715 cm^{-1}. This is due to the presence of a keto carbonyl group. That the compound is not an aldehyde is ascertained by the fact that aldehyde C═O appears in the range of 1,725–1,740 cm^{-1} and aldehyde hydrogen (–CHO) consists of a pair of band in the range 2,700–2,860 cm^{-1}. Appearance of three proton singlet at δ 2.0 in the ^{1}H-NMR spectrum of the molecule suggests the presence of a methyl group on the carbonyl carbon. The nine equivalent protons appearing at δ 1.0 (9 H, s) typical of alkane nature must be attributed to the presence of a *tert*-butyl group. Therefore, the compound is 3,3-dimethyl-2-butanone.



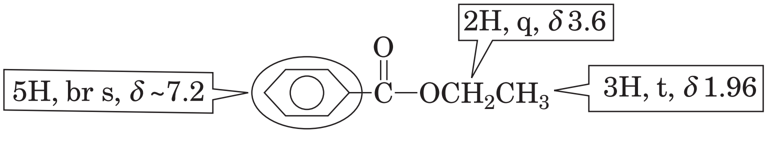
59. A volatile compound (M.F. $C_8H_{18}O$) is transparent above 210 nm in UV region. It shows the following bands in the IR spectrum: (i) 2,851–2,960 (m), (ii) 1,342 (w) and (iii) 1,075 cm^{-1} (s). Only one singlet at δ1.05 is found in its ^{1}H NMR spectrum. Determine the structure of the compound.

Solution Since the compound is transparent above 210 nm in the UV region, it contains no carbonyl group, conjugation, etc. The most characteristic band at 1,075 cm^{-1} (s) in its IR spectrum is due to C—O stretching in C—O—C group. The other bands at 2,851–2,960 cm^{-1} (m) and at 1,342 cm^{-1} (w) are due to C—H stretching and bending respectively. The appearance of one singlet at much upfield (δ 1.05) reveals that all the alkyl groups (six methyl groups) are in exactly similar environment. The following structure is strictly in accordance with the given data.

$(H_3C)_3C—O—C(CH_3)_3$ (Di-*t*-butyl ether)

60. An organic compound (M.F. $C_9H_{12}O_2$) shows three signals in its ^{1}H-NMR spectrum at δ ~7.2(5H, br s), 3.6 (2H, q) and 1.96 (3H, t). One intense IR band appears at 1740 cm^{-1}. Deduce the structure of the compound.

Solution A broad singlet at δ ~ 7.2 indicates the presence of five aromatic protons. The presence of a 2H quartet and a 3H triplet indicates that the compound contains a $—OCH_2CH_3$ group. The intense IR band at 1,740 cm^{-1} is due to the ester C═O group appearing in the range of 1,735–1,750 cm^{-1}. Hence, the following structure is strictly in accordance with the given data.



Ethyl benzoate

61. An organic compound (molecular mass 116) showed the following spectral characteristics:

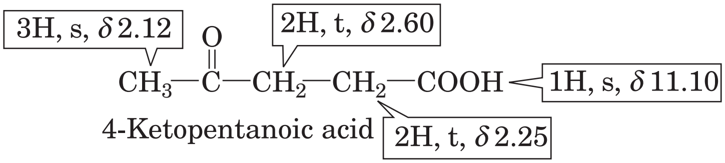
UV: λ_{max} 283 nm (ε_{max} 22)

IR: 2,500 – 300 (b), 1,715 (s), 1,342 cm^{-1} (w)

^{1}H-NMR: δ 2.12 (3H, s), 2.60 (2H, t), 2.25 (2H, t), 11.10 (1H, s)

Determine the structure of the compound.

Solution In the UV spectrum, the absorption at 283 nm of low intensity indicates the presence of a C═O group. Its presence is further confirmed by a strong band at 1,715 cm^{-1}. A very broad band at 2,500–3,000 cm^{-1} is most characteristic of acid O–H stretching and such a band appears as a result of strong H-bonding. Since a very broad O—H stretch band is seen along with a C═O peak, it almost certainly indicates that the compound is a carboxylic acid. The presence of a carboxyl group (—COOH) is further shown by ^{1}H-NMR spectrum; a signal (singlet) is obtained at δ 11.10 (much downfield). Two triplets, one at δ 2.60 and other at δ 2.25, having the same integral area must be due to two methylene groups (—CH_2—CH_2—) under different environments. The appearance of a three H singlet at δ 2.12 must be due to a methyl group attached to the carbonyl group. Hence, the compound having molecular mass 116 is 4-ketopentanoic acid.



$$CH_3—\overset{\overset{\displaystyle O}{\|}}{C}—CH_2—CH_2—COOH$$

4-Ketopentanoic acid

62. An organic compound (molecular mass 130) does not produce iodoform when treated with I_2/NaOH. It showed the following spectral characteristics:

UV: λ_{max} 292 nm (ε_{max} 16)

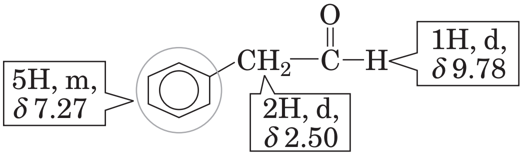
IR: 3,042 (m), 2,941 (w), 2,862 (w), 1,722 (s), 1,605, 1,575 (m), 1,462 cm^{-1} (m)

^{1}H-NMR: δ7.27 (5 H, m), 2.80 (2H, d), 9.78 (1H, t)

Determine the structural formula of the compound.

Solution The UV absorption at 292 nm (ε_{max} 16) is characteristic of a C═O group (an aldehyde or a ketone). The presence of a carbonyl group is further supported by a strong band at 1,722 cm^{-1} in the IR spectrum. That it is due to an aldehyde group is confirmed by the presence of two bands at 2,862 and 2,740 cm^{-1} due to aldehydic C—H stretching.

The absorption bands at 1,605 and 1,575 cm^{-1} indicate an aromatic ring C—C stretch which is further confirmed by a 5H multiplet at δ 7.27 in the ^{1}H-NMR spectrum. The one proton triplet at a lowfield (δ 9.78) is due clearly to the proton of the —CHO group. A two H doublet at δ 2.80 is due to the —CH$_2$— group attached to the aromatic ring. Hence, the structure of the compound is as follows:



Phenylacetaldehyde

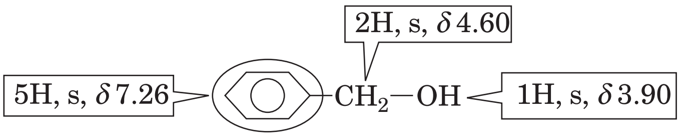
63. An organic compound (molecular mass 108) is not a carboxylic acid. It can be easily oxidised to a crystalline compound (m.p. 122°C). It shows the following spectral characteristics:

UV: λ_{max} 255 nm (ε_{max} 202)
IR: 3,402 (s, br), 3,065 (w), 2,888 (m), 1,499 (w, sh), 1,455 cm^{-1} (m)
^{1}H NMR: δ 3.90 (1H, s), 4.60 (2H, s), 7.26 (5H, s)

Deduce the structure of the compound

Solution The UV absorption at λ_{max} 255 (ε_{max} 202) indicates the presence of benzene ring in the compound.

The appearance of a strong and broad band at 3,402 cm^{-1} is due to N—H or O—H stretching. Since the band is broad, it is more likely to be a H-bonded O—H group. The medium intensity band at 3,065 cm^{-1} is due to aromatic C—H stretching; the bands at 1,499 and 1,455 cm^{-1} are also characteristic of an aromatic ring (C═C). The ^{1}H-NMR spectrum shows three singlets with proton ratio of 1:2:5. If the OH group is present, then one oxygen atom and eight H atoms (1 + 2 + 5) amounts to 24 mass units. The remaining (108 – 24) or 84 mass units correspond to 7 carbon atoms. Therefore, the molecular formula of the compound is C_7H_8O (agrees with molecular mass 108). The five proton singlet at δ 7.26 suggests that the compound is a monosubstituted benzene. The 2H singlet is due to the two benzyl protons (—CH$_2$—Ph). The compound is probably not pure (commercial) and due to spin decoupling both CH$_2$ and OH protons appear as singlet. Hence, the structure of the compound is as follows:



Benzyl alcohol

The compound can easily be oxidized to benzoic acid (m.p. 122°C)

STUDY PROBLEMS

1. How many hertz downfield from the TMS signal would be the signal occurring at 3.0 ppm.

(a) in a 300-MHz spectrometer? (b) in a 500-MHz spectrometer?

2. Where would you expect to find the proton NMR signal of Me_2Mg relative to Me_4Si (TMS) signal?

3. (a) If two signals differ by 1.5 ppm in a 60-MHz spectrometer by how much do they differ in a 300-MHz instrument?

(b) If two signals differ by 90 Hz in a 300-MHz spectrometer, by how much do they differ in a 100-MHz instrument?

[**Hint:** (a) 1.5 ppm; (b) 30 Hz]

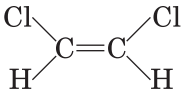
4. A signal sppears at 120 Hz downfield from TMS in a 300-MHz instrument. Calculate the chemical shift of that signal. How many hertz downfield from TMS would the signal be in a 60-MHz instrument?

5. How many signals are expected to be found in the ^{1}H-NMR spectrum of each of the following compounds?

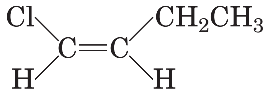
(a) $CH_3CH_2CH_2COCH_3$ (b) $CH_2{=}CH{-}CHO$

(c) $(CH_3)_2CHCH_2CH(CH_3)_2$ (d) $BrCH_2CH_2Br$

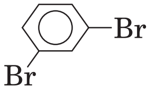
(e)



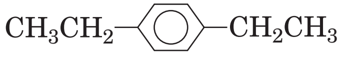
(f)



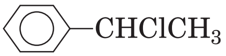
(g)



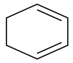
(h)



(i)



(j)



(k) $CH_3CH_2OCH(CH_3)_2$

6. There are three isomeric dibromocyclopropanes. The isomers give ^{1}H-NMR spectrums with one, two and three signals, respectively. Draw the structures of the isomers.

7. Calculate the chemical shift in ppm for each of the following haloalkanes, given their shifts in Hz as measured downfield from TMS on a 60-MHz NMR spectrometer.

(a) Methyl chloride (184 Hz) (b) Bromoform (413 Hz)

(c) Chloroform (437 Hz)

8. Describe the appearance of the proton NMR spectrum of each of the following compounds. How many signals would you expect to find, and into how many peaks will each signal split?

(a) $BrCH_2CH_2OCH_2CH_3$ (b) 1,1,1,2-Tetrachloropropane

(c) $ClCH_2Cl(OC_2H_5)_2$ (d) $CH_3CH_2OCHBrCHBrOCH_2CH_3$

9. Describe the splitting pattern expected for the proton at
(a) C-2 in 2-bromopropanal (b) C-2 in (*Z*)-1,3-dibromopropane

10. All the protons of cyclohexane appear to be equivalent in the NMR spectrum. Why?

11. Deuterium does not give a signal under the conditions of proton NMR spectroscopy. Why?
[**Hint:** The precessional frequency of ^{1}H at a fixed strength of 1.4 tesla is 60 MHz whereas that of ^{2}H at the same field strength is 9.2 MHz.]

12. How many hertz does 1 ppm (one unit on the scale) correspond to an instrument recording proton NMR spectra at
(a) 60 MHz (b) 100 MHz (c) 300 MHz (d) 500 MHz?
[**Hint:** (a) 60 Hz, (b) 100 Hz, (c) 300 Hz, (d) 500 Hz]

13. Predict the chemical shift positions for the protons in (a) methyl acetate (CH_3COOCH_3), (b) ethyl acrylate ($CH_2{=}CHCOOCH_2CH_3$), (c) methyl phenoxyacetate ($C_6H_5OCH_2COOCH_3$)
[**Hint:** (a) The ^{1}H-NMR spectrum of methylacetate shows two signals, at δ 2.0 and δ3.6, respectively. (b) The chemical shift positions for the CH_2 and CH_3 groups are around δ 4.1 and δ 1.3, respectively. The α-hydrogen appears at δ 5.8 and the β-hydrogens appear around δ 6.0. (c) The CH_3 protons appear at δ 3.6. The aromatic protons come to resonance around δ 7.07 (lower frequency by the alkoxy group by approximately 0.2 ppm). The methylene group, flanked by two electronegative groups, appears at δ 4.2 (2.3 ppm for –OPh and 0.7 ppm for –COOR are added to the base value of δ 1.2).]

14. Which of the boldface protons (or sets of protons) has the greater chemical shift, i.e., large δ value?
(a) $CH_3CH_2C\mathbf{H}_2Br$ or $CH_3CH_2C\mathbf{H}_2I$
(b) $CH_3CH_2C\mathbf{H}O$ or $CH_3CH_2COOC\mathbf{H}_3$
(c) $CH_3CH_2C\mathbf{H}_2Br$ or $CH_3CH_2C\mathbf{H}BrCH_3$
(d) $C\mathbf{H}Cl_3$ or $C\mathbf{H}Br_3$

15. Which of the boldface protons (or sets of protons) gives signal at higher frequency (higher δ value)?
(a) $(C\mathbf{H}_3)_2CHOC\mathbf{H}_3$ (b) $C\mathbf{H}_3OC\mathbf{H}_2CH_3$
(c) $C\mathbf{H}_3CCl_2C\mathbf{H}_2Cl$ (d) $CH_3C\mathbf{H}_2CH{=}C\mathbf{H}_2$
(e) $(CH_3)_2C\mathbf{H}COC\mathbf{H}_3$

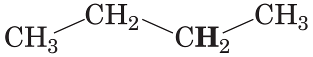
16. Integration could not distinguish between 1,1-dichloroethane (CH_3CHCl_2) and 1,2-dichloro-2-methylpropane (Me_2CClCH_2Cl). Why?
[**Hint:** Integration tells us the relative number of protons that produce each signal, not the absolute number. Both of these two compounds show an integral ratio of 1:3.]

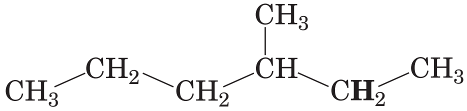
17. Explain how the following three isomeric compounds could be distinguished by their ^{1}H-NMR spectra.

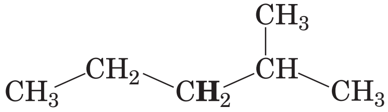
(a) 1,1,1-Trichloropropane (b) 1,1,3-Trichloropropane

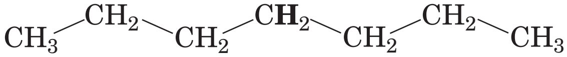
(c) 1,1,2-Trichloropropane

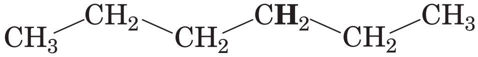
18. How many signals are expected to be appearing for the boldface hydrogens in the ^{1}H-NMR spectrum of the following hydrocarbons?

(a) 

(b) 

(c) 

(d) 

(e) 

[**Hint:** (a) enantiotopic hydrogens: one signal; b) diastereotopic hydrogens: two signals; (c) enantiotopic hydrogens: one signal; (d) neither enantiotopic nor diastereotopic: one signal; (e) enantiotopic: one signal.]

19. Which of the following would show a greater chemical shift for the OH proton and why?

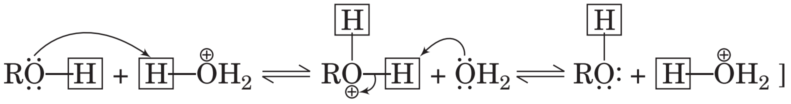
(a) The NMR spectrum of ethyl alcohol dissolved in dichloromethane

(b) The NMR spectrum of pure ethyl alcohol

20. Explain why the signal for the OH proton of a carboxylic acid (RCOOH) appears at a higher frequency (downfield) than that for the OH proton of an alcohol (ROH).

21. Propose mechanisms for acid- and base-catalyzed proton exchange.

[**Hint:** acid-catalyzed proton exchange: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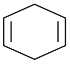
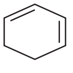
22. How can *o*-, *m*- and *p*-dinitrobenzene be distinguished by proton NMR spectroscopy?

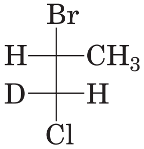
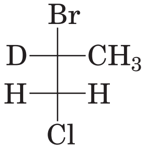
23. How would you distinguish between the compounds in each of the following pairs by ^{1}H-NMR?

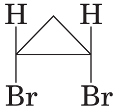
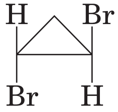
(a)  and 

(b) $ClCH_2CH_2CH_2Cl$ and $ClCH_2CH_2CH_2NO_2$

(c) $CH_3CH_2CH_2OCH_3$ and $(CH_3CH_2)_2O$

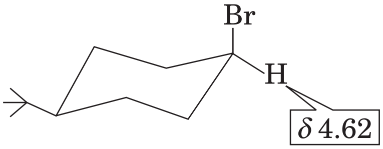
(d) $(CH_3)_3CCOOCH_3$ and $(CH_3)_2C(OCH_3)_2$

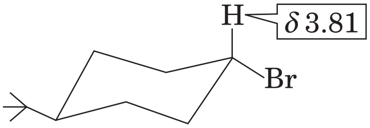
(e)  and 

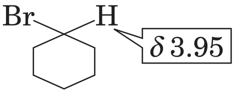
(f)  and 

[**Hint:** (a) 2 signals and 3 signals respectively; (f) 3 signals and 2 signals, respectively]

24. From the following data, estimate the percentages of axial and equatorial forms present in bromocyclohexane.







25. In PhCHO, two of the ring protons come to resonance at δ 7.87 ppm, and the other three ring protons come to resonance in the range from δ 7.5 to 7.6 ppm. Explain.

26. The position of the signal for the OH proton of phenol is concentration dependent. However, the OH proton of *o*-hydroxyacetophenone, which appears at δ 12.05 ppm, does not show any great shift upon dilution. Explain these observations.

27. The methyl protons of acetonitrile (CH_3CN) appear at δ 1.97, whereas that of methyl chloride (CH_3Cl) appear at δ 3.05, even though the dipole moment (μ) of acetonitrile is 3.92D and that of methyl chloride is only 1.85 D. From the dipole moment values it becomes evident that the electronegativity of the cyano group is greater than that of the Cl atom. Explain why the methyl protons of acetonitrile are actually more shielded than those in methyl chloride, in contrast with the results expected on the basis of electronegativity.

[**Hint:** Diamagnetic anisotropy in CH_3CN.]

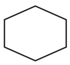
28. Arrange the following compounds in increasing order of shielding of methyl protons and give your reasoning:

CH_3F, $(CH_3)_3N$, $CH_3CH_3CH_3OCH_3$, $(CH_3)_2Mg$

29. In which of the following two solutions the δ value of the OH proton of ethanol will be higher?

(a) a 2 M solution (b) a 0.2 M solution

30. Two isomeric hydrocarbons A and B (M.F.: C_6H_{12}) exhibit sharp singlets at δ 1.70 and 1.40, respectively. A decolourises bromine-water, wehreas B does not. Identify A and B.

[**Hint:** A ⇒ $(CH_3)_2C{=}C(CH_3)_2$; B ⇒ ]

31. How can NMR spectroscopy be used for quantitative estimation of *keto* and *enol* tautomers?

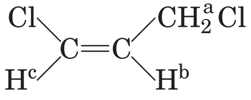
32. How would you explain the appearance of a 3H triplet and a 2H quartet in CH_3–CH_2–group? Give the relative intensities of various peaks in these multiplets.

33. Acetylene protons are nore shielded than ethylene protons. Explain.

34. Name some important solvents used in ^{1}H-NMR spectroscopy. What are the important characteristics of the solvents to be used in this spectroscopic technique?

35. Explain why TMS is used as a standard reference in ^{1}H-NMR spectrocopy.

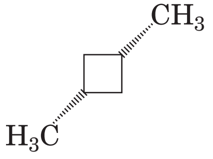
36. Draw a splitting diagram for the H^b proton if $J_{bc} = 10$ and $J_{ba} = 5$.

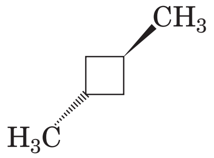


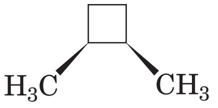
37. How could proton NMR be used to establish that the addition of HBr to propene follows Markowikoff's rule?
[**Hint:** The product (Me_2CHBr) gives two NMR signals.]

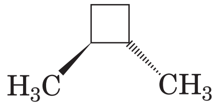
38. Write the possible structures of the esters having molecular formula $C_4H_8O_2$. How can these esters be distinguished by ^{1}H-NMR spectral analysis?

39. How many signals are expected to be obtained in the ^{1}H-NMR spectrum of each of the following compounds?

(a)


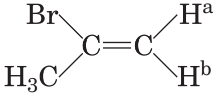
(b)


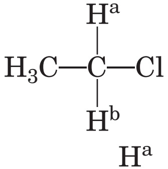
(c)


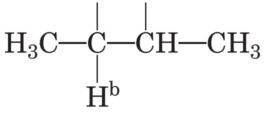
(d)


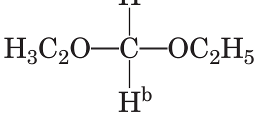
[**Hint:** Signals: (a) ⇒ 4; (b) ⇒ 3; (c) ⇒ 4; (d) ⇒ 4.]

40. Determine whether the labelled protons in each case are expected to have identical or different chemical shifts.

(a)


(b)

$H_3C-\underset{H^b}{\overset{H^a}{C}}-Cl$

(c)

$H_3C-\underset{H^b}{\overset{H^a}{C}}-\overset{Br}{CH}-CH_3$

(d)

$H_3C_2O-\underset{H^b}{\overset{H^a}{C}}-OC_2H_5$

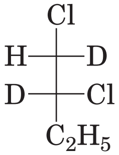
[**Hint:** (a) diastereotopic: different chemical shift; (b) enantiotopic: identical chemical shift; (c) diastereotopic: different chemical shift; (d) homotopic: identical chemical shift.]

41. Explain how the ^{1}H-NMR spectrum of the compounds within each of the following sets would differ.

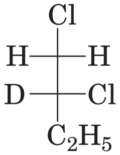
(a) $(CH_3)_2CHCl$ and $(CH_3)_2CDCl$

(b) $ClCD_2CH_2CH_2Cl$ and $ClCH_2CH_2CH_2Cl$

(c)



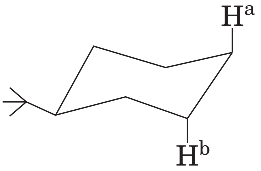
and



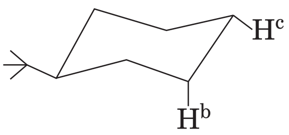
[**Hint:** Deuterium does not give a signal under the conditions of proton NMR spectroscopy.]

42. What is the dihedral angle and expected coupling constant (J) between the labelled protons in each of the following molecules?

(a)



(b)



43. How would the ^{1}H-NMR spectrum of ethyl fluoride (CH_3CH_2F) differ from that of ethyl chloride (CH_3CH_2Cl)?

[**Hint:** Compounds containing fluorine will show spin-spin splitting due to coupling between the fluorine and the hydrogen on either the same of the adjacent carbon atom. Since the spin of fluorine (^{19}F) is 1/2, the n+1 Rule can be used to predict the multiplicities of the attached protons. Other halogens do not cause spin-spin splitting.]

44. Predict the ^{1}H-NMR spectrum expected for the $Cl_2CHCHClCHCl_2$ molecule:

45. A signal at δ 7.3 is found in the ^{1}H-NMR spectrum of chloroform in cyclohexane. The signal shifts to δ 5.74 when the spectrum is run in benzene. Explain.

[**Hint:** Benzene behaves as a Lewis base to chloroform and considerable charge transfer is responsible for shielding the proton. Also, the diamagnetic shielding effect of the ring current of benzene nucleus is partly responsible as the H atom of $CHCl_3$ is located in the vertical zone of the ring.]

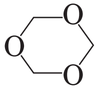
46. Explain why ^{1}H-NMR signal for the OH proton in *o*-hydroxyacetophenone shifts to lower δ when temperature is increased.

47. What kind of proton NMR spectrum would you expect to obtain from undecadeuteriocyclohexane at room temperature?

48. Sketch the proton NMR spectra that you would expect from each of the following compounds: (a) $CH_3\ CF_2CH_3$, (b) CH_3CF_2Cl, (c) CH_3CFCl_2 and (d) CH_3CF_3.

49. The proton magnetic resonance spectrum of CH_3F contains two lines. What must you conclude?

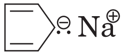
50. 1,3,5-Trioxane exists in chair conformation similar to that of cyclohexane.



What is the expected appearance of its NMR spectrum at room temperature and –100°C.

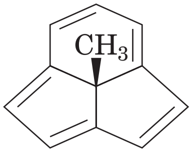
51. Explain the following observations:

(a) The NMR spectrum of the sodium salt of cyclopentadiene (I) consists of a singlet.



I

(b) The methyl group in the following compound has an unusual chemical shift of δ –1.67, about 4 ppm lower than the chemical shift of a typical allylic methyl group.



52. What is the difference in ^{1}H-NMR spectrum of (a) pure ethanol and (b) ethanol containing a trace of acid?

53. Compare the ^{1}H-NMR spectra of CH_3CH_2Cl and CH_3CHDCl.

54. Predict the structural units of a molecule which are responsible for the appearance of:

(a) A triplet and a quartet
(b) Two doublets
(c) A doublet and a quintet
(d) Two triplets of equal integral area

Conjoint IR–UV–NMR Spectrometry Problems

55. An organic compound (M.F. $C_9H_{10}O_2$) showed the following spectral characteristics:

UV: λ_{max} 270 nm
IR: 1,680 cm^{-1}
^{1}H-NMR: δ 7.6(2H, d, J = 8Hz), 6.9(2H, d, J = 8 Hz), 3.9 (3H, s), 2.0 (3H, s)

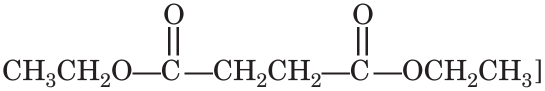
Determine the structure of the compound.

[**Hint:** *p*-$MeC_6H_4COCH_3$]

56. An organic compound (Mol.wt. 174) showed the following spectral characteristics:

UV: λ_{max} 213 nm (ε_{max} 60)
IR: 2,857–2,941 (m), 1,745 (s), 1,458 cm^{-1} (m)
^{1}H-NMR: δ 4.14 (4H, q, J = 7.2 Hz), 2.60 (4H, s), 1.57(6H, t, J = 7.2 Hz)

Deduce the structure of the compound.

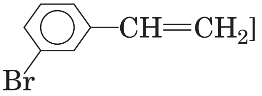
[**Hint:** 
$CH_3CH_2O-\overset{\overset{O}{\|}}{C}-CH_2CH_2-\overset{\overset{O}{\|}}{C}-OCH_2CH_3$]

57. An organic compound (M.F. C_7H_8Br) produces a 1° alcohol on hydroboration–oxidation. The spectral data of the compound is given below:

UV: λ_{max} 282 nm (ε_{max} 450).

IR: 3,033 (m), 1,646 (m), 1,602 (m), 1,582 (U), 820 (s) and 710 cm^{-1} (m).

^{1}H-NMR: δ 7.26 – 7.38 (4H, asymmetrical pattern), 5.70 (1H, doublet of doublets), 6.70 (1H, doublet of doublets) and 5.14 (1H, doublet of doublets). Deduce the structure of the compound.

[**Hint:** 

58. A compound (M.F. C_3H_7NO) gives the following spectral data:

UV: λ_{max} 238 nm (ε_{max} 10500)

IR: 3,428 (m), 2,857–2,941 (W), 1,680 (s) and 1,452 cm^{-1} (w)

^{1}H-NMR: δ 8.13 (1H, s), 2.70 (3H, s), and 1.90 (3H, s)

Deduce the structure of the compound.

[**Hint:** $CH_3CONHCH_3$]

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4. Bhacca, N. S.; Williams, D. H. *Applications of NMR Spectroscopy in Organic Chemistry*; Holden-Day, Inc., 1964.
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Polynuclear Hydrocarbons

5

Chapter Outline

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  5.1.2 Structure of Naphthalene
  5.1.3 Synthesis of Naphthalene
  5.1.4 Physical Properties of Naphthalene
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5.2 Anthracene and Its Derivatives
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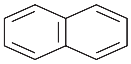
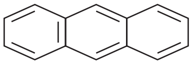
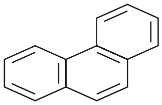
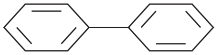
INTRODUCTION

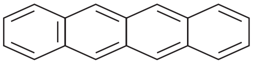
Polynuclear hydrocarbons are hydrocarbons that are composed of multiple aromatic rings. These are of two types: (i) in some of them two or more benzene rings are joined to each other either directly or through carbon chains; they include compounds like biphenyl, diphenylmethane, etc. and (ii) in rest of them two or more rings are fused together in the *o*-positions, e.g., naphthalene, anthracene, phenanthrene, etc. Structures of some polynuclear hydrocarbons are given below:


Naphthalane

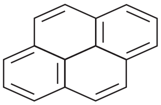

Anthracene


Phenanthrene

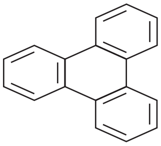

Biphenyl



Naphthacene



Pyrene



Triphenylene

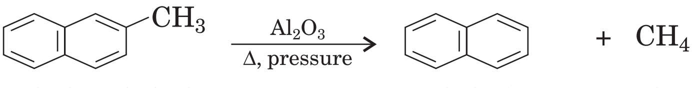
The study of condensed polynuclear hydrocarbons has assumed great importance as a large number of them has been found to have carcinogenic property (e.g., 1,2-benzanthracene derivatives like 5,6-dimethyl-1,2-benzanthracene, 3,4-benzpyrene, etc.). Although the exact nature of structure–activity relationship has not yet fully understood, the possibility of such a correlation has inspired scientists to carry out research in the synthesis of this class of compounds. The chemistry of naphthalene, anthracene and phenanthrene are described in this chapter as representative molecules.

5.1 NAPHTHALENE AND ITS DERIVATIVES

Naphthalene, $C_{10}H_8$, is the largest constituent of coal-tar (97%). It can be isolated from coal-tar and petroleum.

Isolation from coal-tar Naphthalene crystallizes out as a solid substance when heavy and middle oil fractions of the coal tar distillation are cooled. Solid naphthalene is filtered, melted, washed with concentrated sulphuric acid (to remove basic impurities like pyridine and pyrrole), washed with water and then treated with aqueous sodium hydroxide (to remove acidic impurities like phenols). Again it is washed with water and finally purified by distillation.

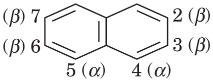
Isolation from petroleum Naphthalene is also being made synthetically from petroleum. When a selected fraction of petroleum is passed over a heated catalyst, e.g., copper or platinum at 680°C at atmospheric pressure, naphthalene and methylnaphthalenes are obtained. The latter are converted to naphthalene by heating with hydrogen under pressure in the presence of a metal oxide catalyst. This process is known as *hydrodealkylation*.



2-Methylnaphthalene Naphthalene Methane

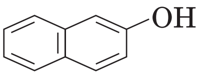
5.1.1 Nomenclature and Isomerism

Various positions of naphthalene are numbered as follows:

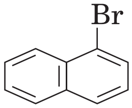


Naphthalene

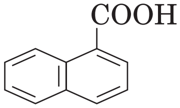
In this structure, the positions 1, 4, 5 and 8 are equivalent and are also designated by the Greek letter α. Similarly, the remaining positions 2, 3, 6 and 7 are identical and designated by the Greek letter β. It thus follows that naphthalene forms only two monosubstitution products, e.g., α- or 1-nitronaphthalene and β- or 2-nitronaphthalene. Ten disubstituted products are possible if two substituents are identical. However, if the two substituents are not identical, 14 isomeric disubstituted products are possible. The position of single substituent in simple naphthalene derivatives are usually represented by the Greek letters. However, it is better to use numerals, especially in the case of di- and polysubstituted naphthalenes.



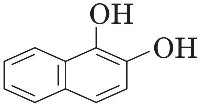
β-Naphthol



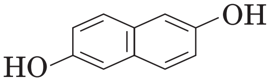
α-Bromonaphthalene



α-Naphthoic acid



1,2-Dihydroxynaphthalene

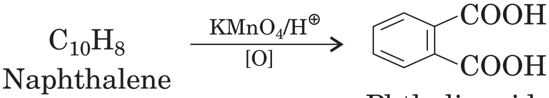


2,6-Dihydroxynaphthalene

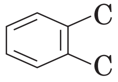
5.1.2 Structure of Naphthalene

The structure of naphthalene has been established from the following facts and conclusions therefrom:

1. Elemental analysis and molecular mass determination suggest that the molecular formula of naphthalene is $C_{10}H_8$.
2. Naphthalene is an aromatic compound because its properties resemble those of benzene (it undergoes electrophilic substitution reactions, it resists addition reactions, etc.) and the structure obeys Huckel's rule of aromaticity [a planar conjugated cyclic system having $(4n + 2)\pi$ electron, where $n = 2$].
3. When naphthalene is completely hydrogenated, decaline ($C_{10}H_{18}$) is obtained. This observation suggests that it has five double bonds.
4. When naphthalene is subjected to vigorous oxidation, it gives phthalic acid. This observation suggests that in naphthalene there is at least one benzene ring with two side chains (A) in the *ortho*-positions.

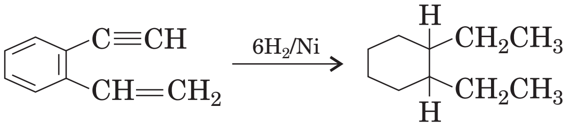


Phthalic acid



(A)

Two independent unsaturated side chains containing four C-atoms and four H-atoms can be written as shown below (B). However, this structure of naphthalene consumes 6 moles of hydrogen, whereas naphthalene consumes only 5 moles of hydrogen.

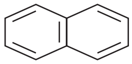


B
($C_{10}H_8$)

($C_{10}H_{20}$)

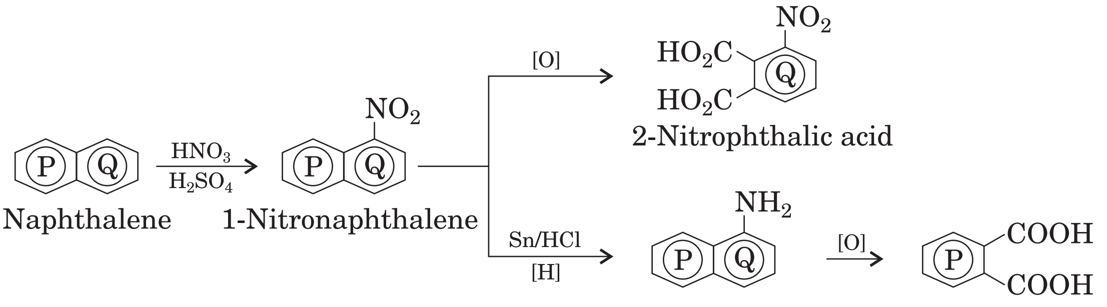
; $\underset{(C_{10}H_8)}{\text{Naphthalene}} \longrightarrow C_{10}H_{18}$

Therefore, B is not the actual structure of naphthalene. On the basis of the above observations and analogy with the Kekule formulation of benzene, Erlenmeyer proposed structure I for naphthalene in which two benzene rings are fused together at *ortho*-positions.

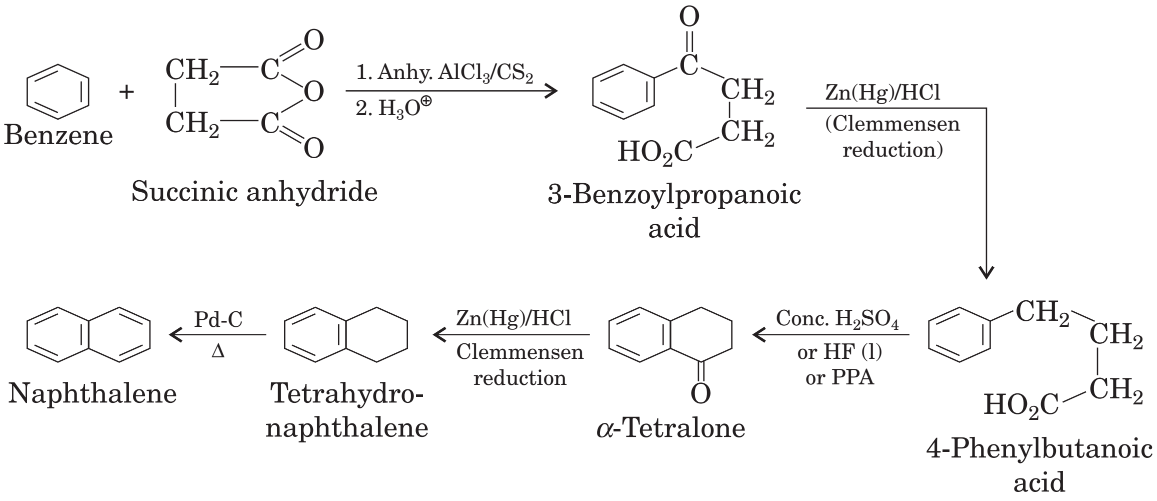


I

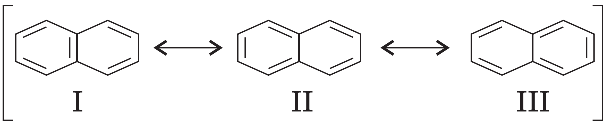
That I is the actual structure of naphthalene has been confirmed on the basis of the following experiments. On nitration, naphthalene yields 1-nitronaphthalene, which on oxidation produces *o*-nitrophthalic acid. The electron-attracting —NO_2 group withdraws electron from the ring to which it is attached and thereby makes the ring less susceptible to oxidation. The relatively electron-rich other ring undergoes oxidation to yield 2-nitrophathalic acid. When 1-nitronaphthalene is reduced with Sn/HCl, 1-aminonaphthalene is obtained. The amino group by its +R effect makes the ring attached to it relatively electron-rich. When 1-aminonaphthalene is oxidized, phathalic acid is obtained. Therefore, the beneze ring in phthalic acid obtained by oxidation of 1-aminonaphthalene is not the same ring as that originally containing the —NO_2 group in 1-nitronaphthalene, i.e., there are two benzene rings in naphthalene which are *ortho*-fused.



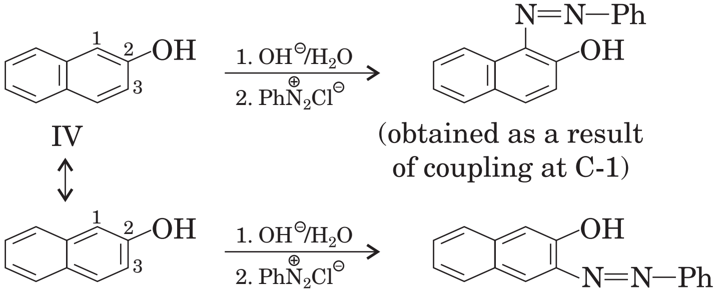
The structure of naphthalene has been confirmed by several unambiguous synthesis. One very important method is Haworth synthesis which starts with a Friedel-Crafts reaction involving benzene and succinic anhydride (succinoylation) in the presence of anhydrous $AlCl_3$ to yield 3-benzoylpropanoic acid. This acid upon Clemmensen reduction followed by ring closure with concentrated sulphuric acid (another Friedel-Crafts acylation) gives α-tetralone. When α-tetralone is subjected to Clemmensen reduction followed by dehydrogenation using palladized charcoal or selenium, naphthalene is obtained.



Naphthalene has a fixed bond structure Physicochemical evidence like heat of hydrogenation and heat of combustion of naphthalene suggest that the molecule is a resonance hybrid of the following three neutral canonicals or resonance structures (I, II and III).



In the symmetrical structure I, both the rings are benzenoid (benzene-like), whereas in the unsymmetrical structures II and III, one of the two rings is *o*-quinonoid (quinone-like) in nature. On the basis of the fact that quinones are more reactive (less stable) than benzene, Fries formulated a rule, called 'Fries rule' which states that the most stable form or resonance structure of a polynuclear hydrocarbon is that in which maximum number of rings are present in the benzenoid form. Therefore, according to the Fries rule, the structure I is expected to make the highest contribution towards the stability of naphthalene, i.e., towards the resonance hybrid. The fixed bond character of naphthalene is observed in the coupling reaction of β-naphthol. Benzenediazonium cation couples with alkaline solution of β-naphthol to form an azo dye. The coupling reaction is found to take place always at C-1, but never at C-3. For coupling reaction to take place $>C=C\!<^{OH}$ moiety is required. In structure IV, this is present when C-1 is considered as the site of attack in β-naphthol. In the case of the resonance structure V, the coupling is expected to take place at C-3, but this has not been observed. Therefore, naphthalene reacts through its fixed bond structure I.



IV

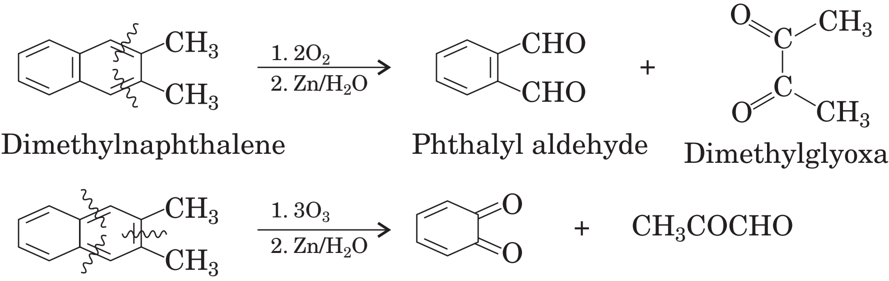
V

β-Naphthol

(obtained as a result of coupling at C-1)

(C-3 coupling product not obtained)

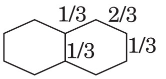
The presence of almost a single structure for naphthalene has been supported by the fact that 2,3-dimethylnaphthalene undergoes ozonolysis to yield a mixture of phthalyl aldehyde and dimethylglyoxal nearly exclusively. *o*-Benzoquinone and methylglyoxal are formed in negligible amounts.



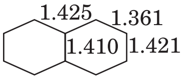
2,3-Dimethylnaphthalene Phthalyl aldehyde Dimethylglyoxal

2,3-Dimethylnaphthalene *o*-Benzoquinone Methylglyoxal

The double bond character of the various bonds in naphthalene is shown in structure (IV), and are obtained by taking the average of the three resonating structures (I–III) on the assumption that all of them contribute equally to the resonance hybrid. Thus, 1,2-bond is expected to be shorter than the 2,3-bond. This has been proved to be correct by X-ray and electron-diffraction analysis (see structure V; bond length in Å units).



IV



V

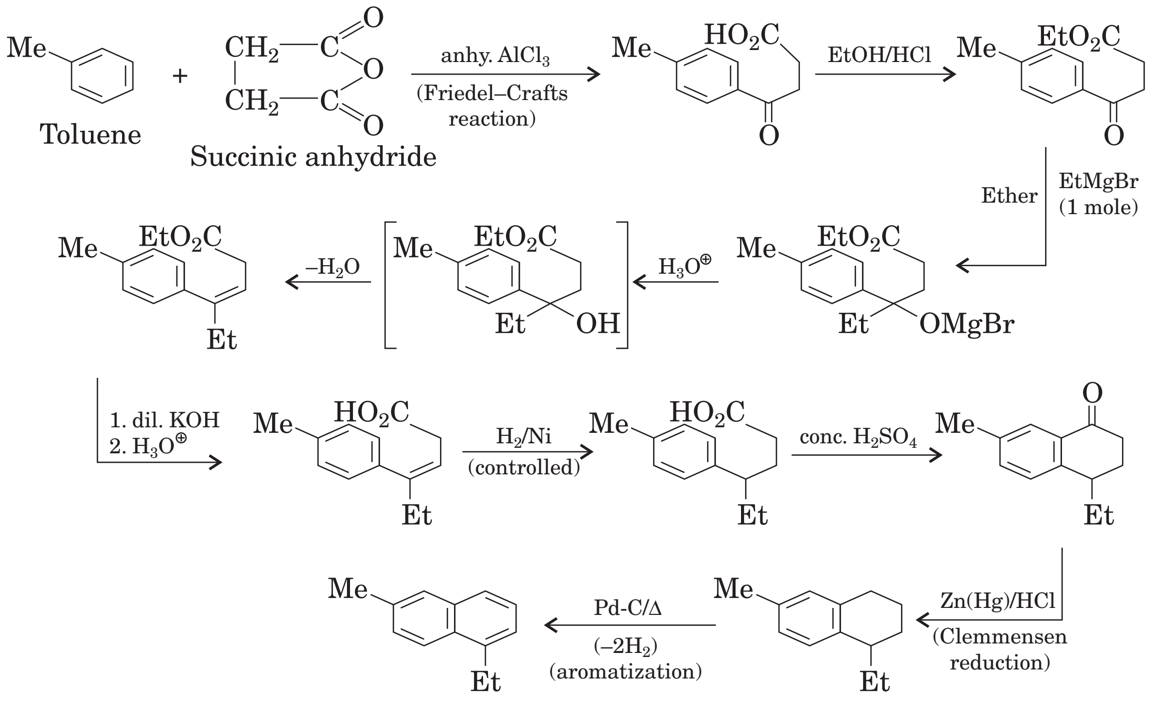
5.1.3 Synthesis of Naphthalene

Naphthalene and its derivatives can be synthesized by the following methods:

5.1.3.1 Haworth Synthesis

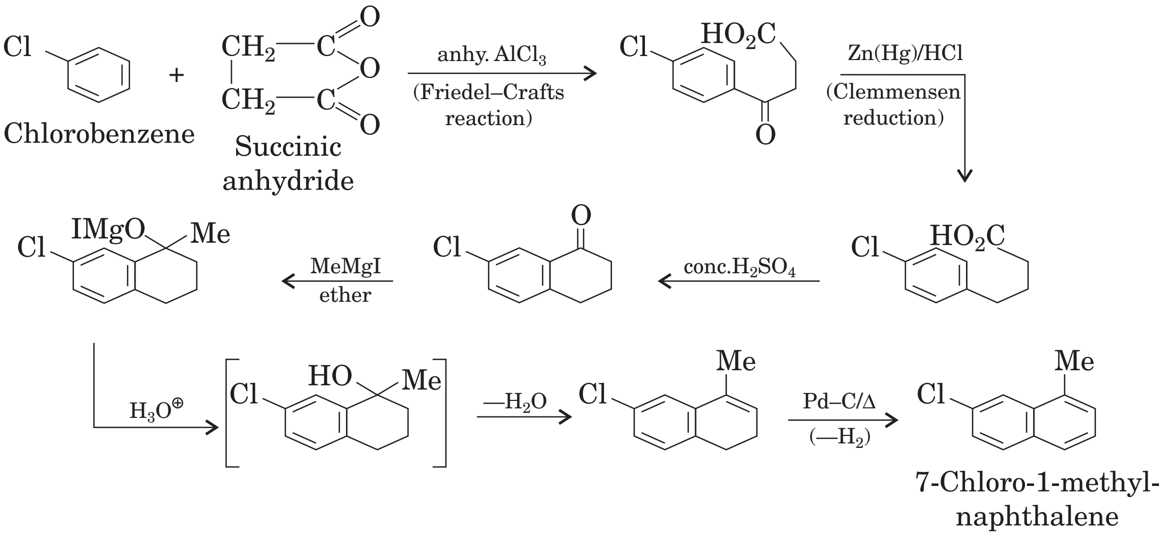
Synthesis of naphthalene by this method has already been discussed. Synthesis of some of its derivatives are outlined as follows:

(a) 1-Ethyl-6-methylnaphthalene

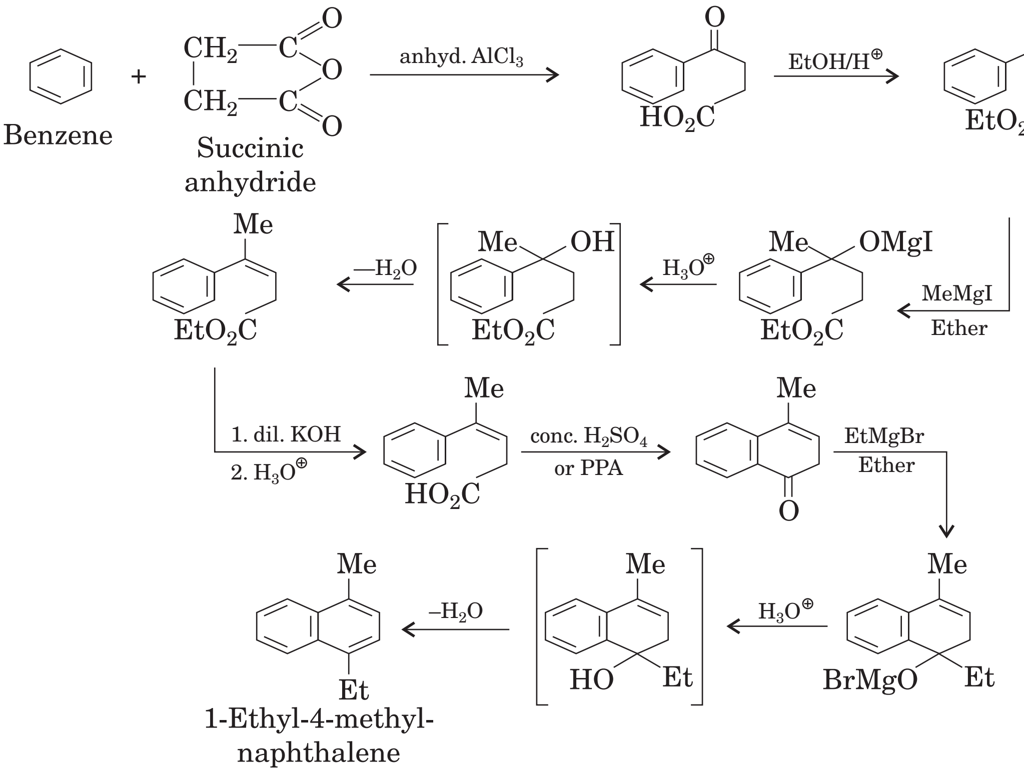


1-Ethyl-6-methylnaphthalene

(b) 7-Chloro-1-methylnaphthalene

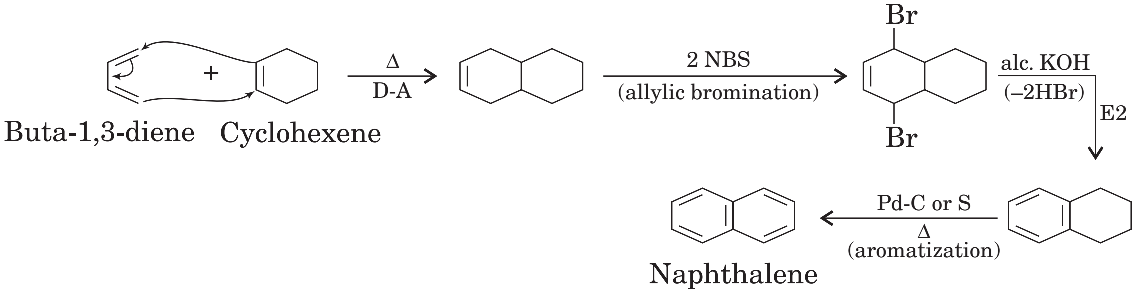


(c) 1-Ethyl-4-methylnaphthalene

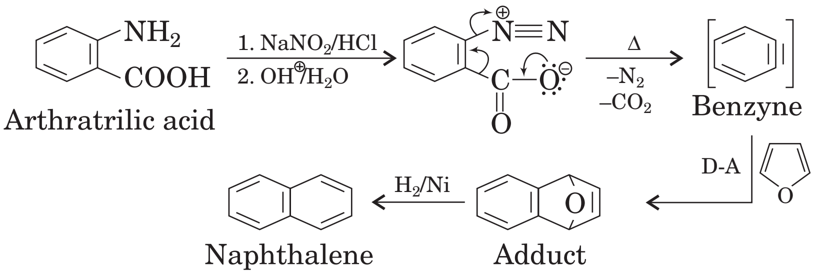


5.1.3.2 Synthesis by the Diels–Alder Reaction

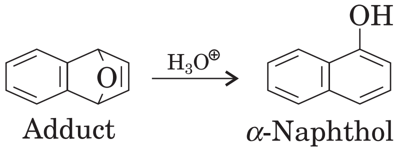
Cyclohexene reacts with buta-1,3-diene to form a Diels–Alder adduct. The adduct is then treated with two equivalents of *N*-bromosuccinimide (NBS) to yield a dibromo derivative (allylic bromination). The dibromide is treated with alcoholic KOH to yield tetraline. Dehydrogenation of tetraline with Pd-C produces naphthalene.



Naphthalene may also be prepared by treating the Diels–Alder adduct of furan and benzyne with H_2/N_2.

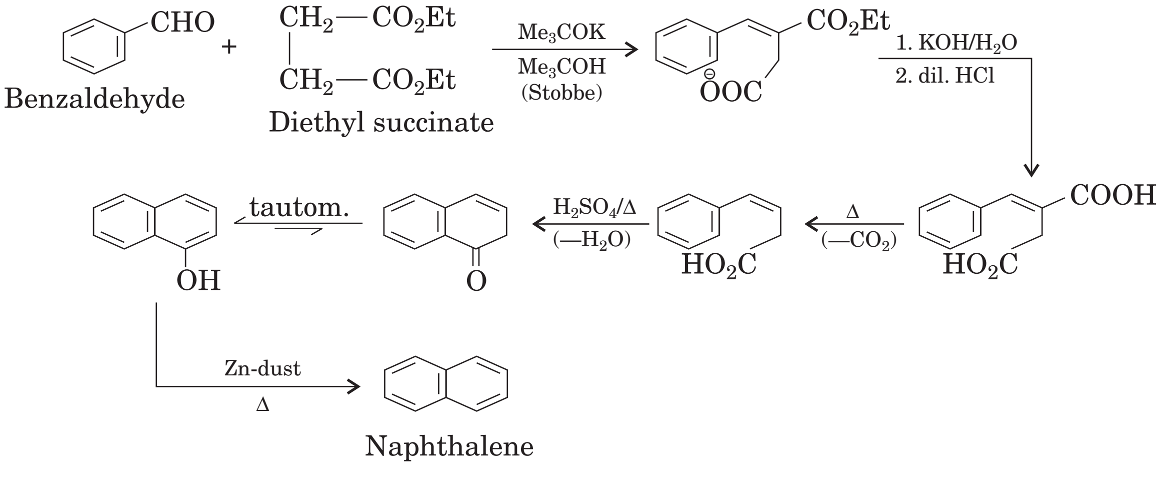


When the Diels–Alder Adduct is subjected to acid-hydrolysis, α-naphthlol is obtained.



5.1.3.3 *Fittig and Erdmann Synthesis*

Benzaldehyde is allowed to react with diethyl succinate to form an alkylidene succinic acid ester (salt). This product of Stobbe condensation is then hydrolyzed to give a dicarboxylic acid. It is decarboxylated by heating to yield 4-phenyl-3-butenoic acid. This acid is cyclized by treating with concentrated H_2SO_4 to yield α-naphthol which on zinc dust distillation produces naphthalene.



5.1.4 Physical Properties of Naphthalene

Naphthalene is a solid crystalline substance having melting point 80°C and possesses a characteristic odour. It sublimes readily on heating. It is used as an insecticide and in the preparation of phthalic anhydride including dyes.

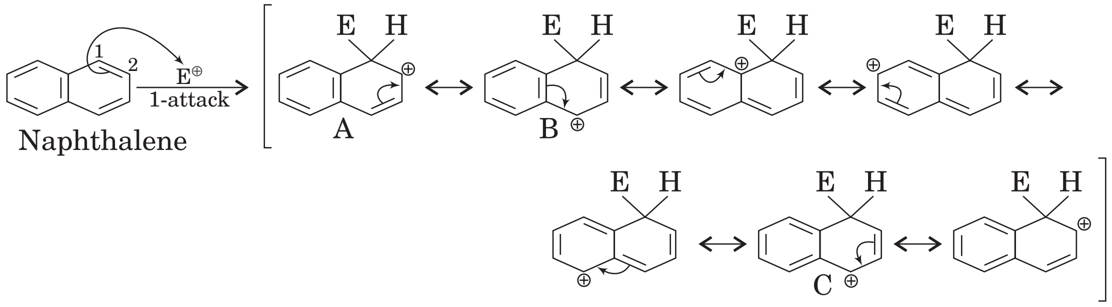
5.1.5 Chemical Properties of Naphthalene

Naphthalene is an aromatic compound. Since it contains two benzene rings, it might have been expected that the resonance energy of naphthalene would be close to 72 kcal/mol. However, its resonance energy is 61 kcal/mol, i.e., 30.5 kcal/mol per benzene ring on the average. Hence, naphthalene is less aromatic than benzene. Consequently, naphthalene possesses less aromatic character than benzene and so it is expected to be more reactive than benzene.

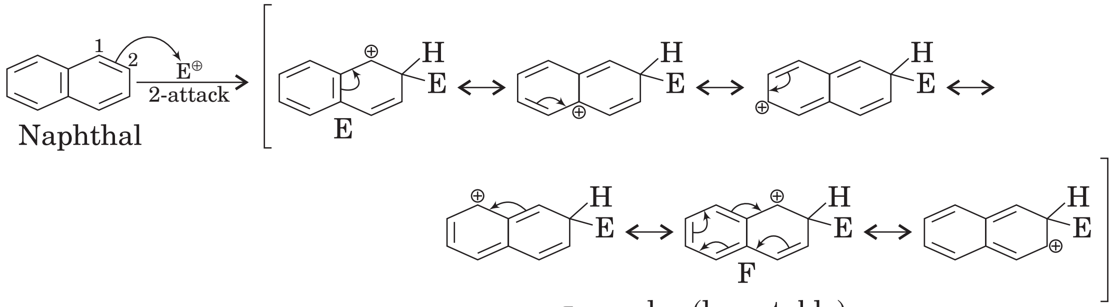
Reactions Naphthalene, a typical aromatic hydrocarbon, undergoes electrophilic substitution reactions like benzene. It also undergoes oxidation and reduction more readily than benzene in respect of only one ring. Some of the reactions of naphthalene are discussed below.

5.1.5.1 Electrophilic Substitutions

Naphthalene undergoes electrophilic substitution preferentially at 1-position. This observation can be well explained in terms of relative stabilities of carbocation intermediates or σ-complexes involved in 1- and 2-suibstitution processes. The resonance structures drawn for the carbocation intermediates or σ-complexes for 1- and 2-attack are as follows:



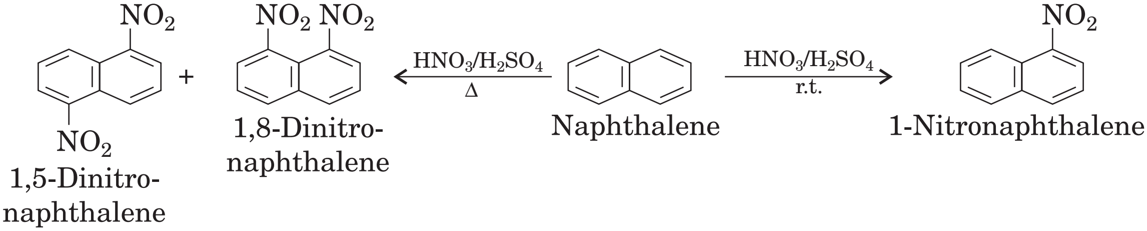
σ-complex (more stable)



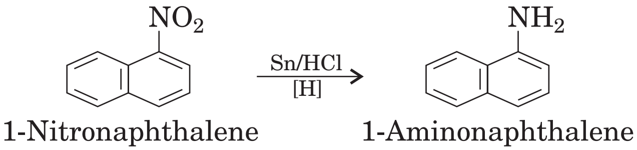
σ-complex (less stable)

The resonance hybrid of the carbocation intermediate or σ-complex for 1-attack contains seven resonance structures. In four of them (A, B, C and D), the aromatic sexlet is preserved in one benzene ring (R.E. 36 kcal/mol). On the other hand, the resonance hybrid of the carbocation intermediate for 2-attack contains six resonance structures. Of these six, only two (E and F) contain intact benzene rings. Structures lacking the intact benzene ring are not aromatic and are thus less stable. It thus follows that the intermediate carbocation or σ-complex for 1-attack is relatively more stable than for 2-attack. As a consequence, substitution at 1-position occurs more rapidly and predominantly.

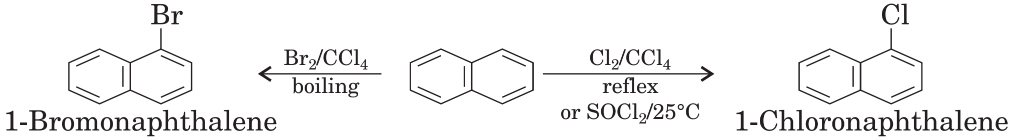
(a) Nitration When naphthalene is treated with a mixture of concentrated nitric acid and concentrated sulphuric acid, 1-nitronaphthalene is obtained. However, when the reaction is carried out at higher temperature, a mixture of 1,5-and 1,8-dinitronaphthalenes are formed.



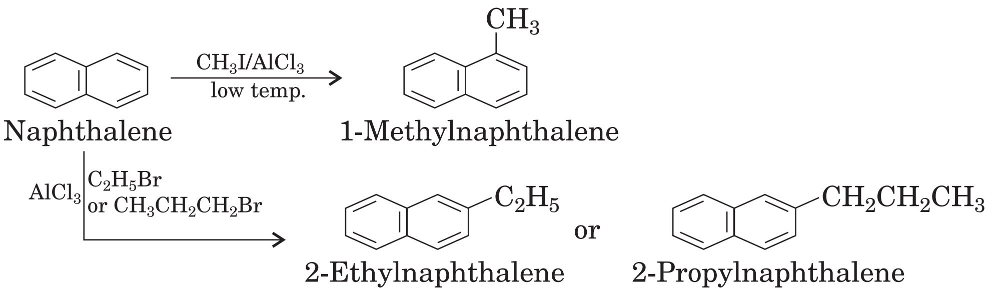
When 1-nitronaphthalene is reduced with metallic tin and concentrated hydrochloric acid, α-naphthylamine or 1-aminonaphthalene is obtained.



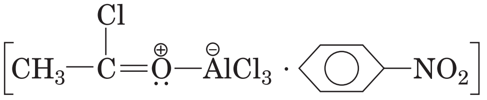
(b) Halogenation Chlorination and bromination of naphthalene takes place readily and unlike benzene no Lewis acid catalyst is required. The reaction occurs almost exclusively at 1-position.



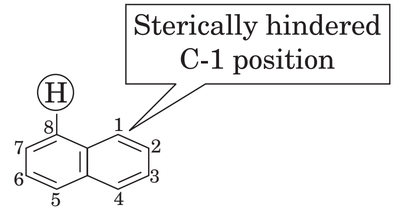
(c) Friedel–Crafts alkylation This reaction should be carried out under mild conditions of temperature, since at higher temperature binaphthyl is the major product. The amount of 1- and 2-substituted products depends on the size of the reagent. For instance when methyl iodide is used as the alkylating agent, a mixture of 1- and 2-substituted naphthalenes with the dominance of the 1-isomer is obtained. However, when ethyl or *n*-propyl bromide is used, only the 2-isomer is obtained. This is because of steric interaction between the bulkier reagent and the hydrogen at the *peri*-position (8-position).



(d) Friedel–Crafts Acylation Although the 1-position of naphthalene is the favourable position for electrophilic attack, this position is sterically more hindered to the H atom on the adjacent vertex of the second ring (*peri*- or 8-position). Acylation in nitrobenzene (solvent) involves the bulky complex I which has a large steric demand. For this reason, acylation of naphthalene, when carried out in nitrobenzene, produces 2-acetylnaphthalene as the major product (95%).

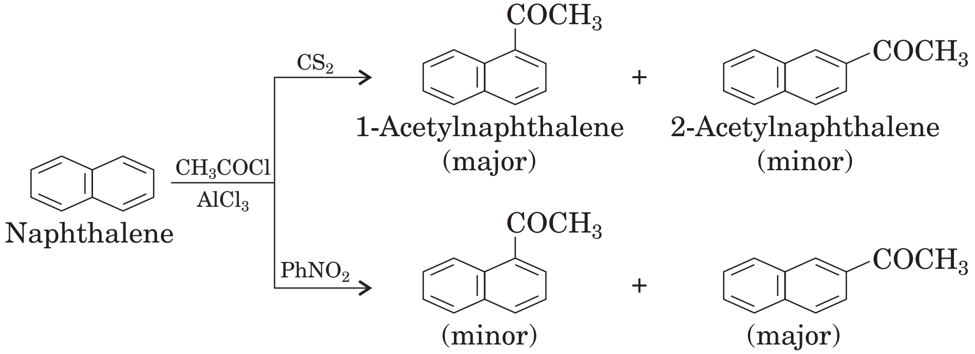


I

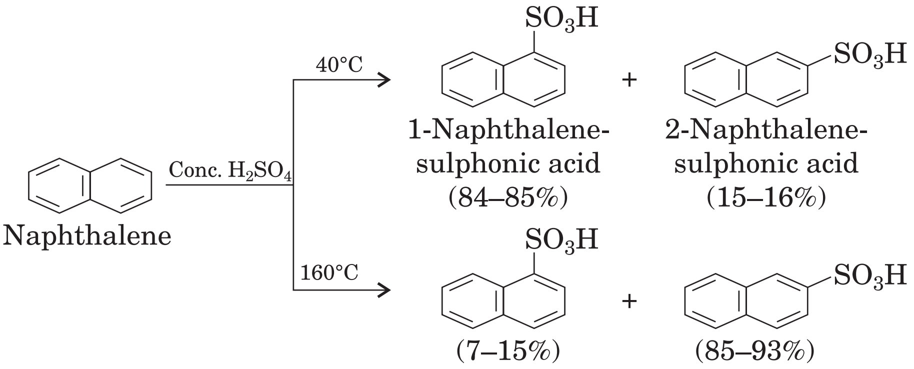


Naphthalene

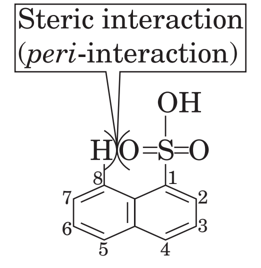
On the other hand, the complex involved in acylation carried out in CS_2 is not so bulky and because of this, 1-acetylnaphthalene is obtained as the major product (75%).



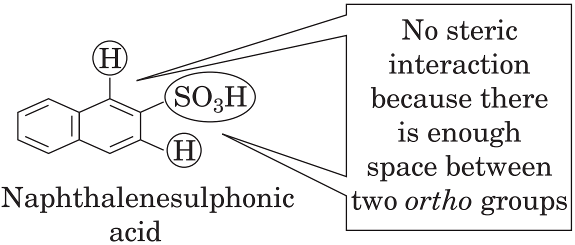
(e) Sulphonation Sulphonation of naphthalene under mild conditions gives mainly 1-naphthalenesulphonic acid, while its sulphonation under more vigorous conditions give mostly 2-naphthalenesulphonic acid.



The sulphonation of naphthalene is readily reversible at an elevated temperature, whereas at low temperature the reaction is practically irreversible. Sulphonation at low temperature (40°C) gives mainly the 1-substitution product. Since the reaction does not reach equilibrium at this temperature, the product isolated is one that formed at a faster rate (kinetic product). Due to greater stabilization of the intermediate carbocation involved in the rate-determining step of 1-substitution reaction, the 1-acid is formed rapidly. Although the 1-acid is formed more rapidly, it is thermodynamically less stable than the 2-acid. The can be explained in terms of steric strain (van der Waals repulsions) that occurs between the groups in the 1- and 8-positions. The sulphonic acid group is much larger in size (as large as a *tert*-butyl group). The unfavourable steric interaction between this group and the H-atom in the 8-position, called a *peri*-interaction, destabilizes the 1-acid.



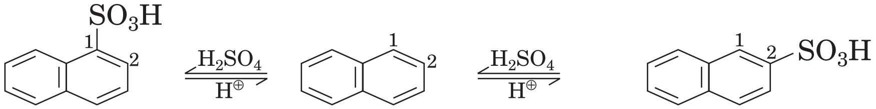
1-Naphthalenesulphonic acid (less stable)


H
SO_3H
H
No steric interaction because there is enough space between two *ortho* groups

2-Naphthalenesulphonic acid (more stable)

A *peri*-interaction is much more severe than the interaction of the same two groups in *ortho*-positions because bonds in *ortho*-positions diverge from each other, whereas the bonds in *peri*-positions are parallel.

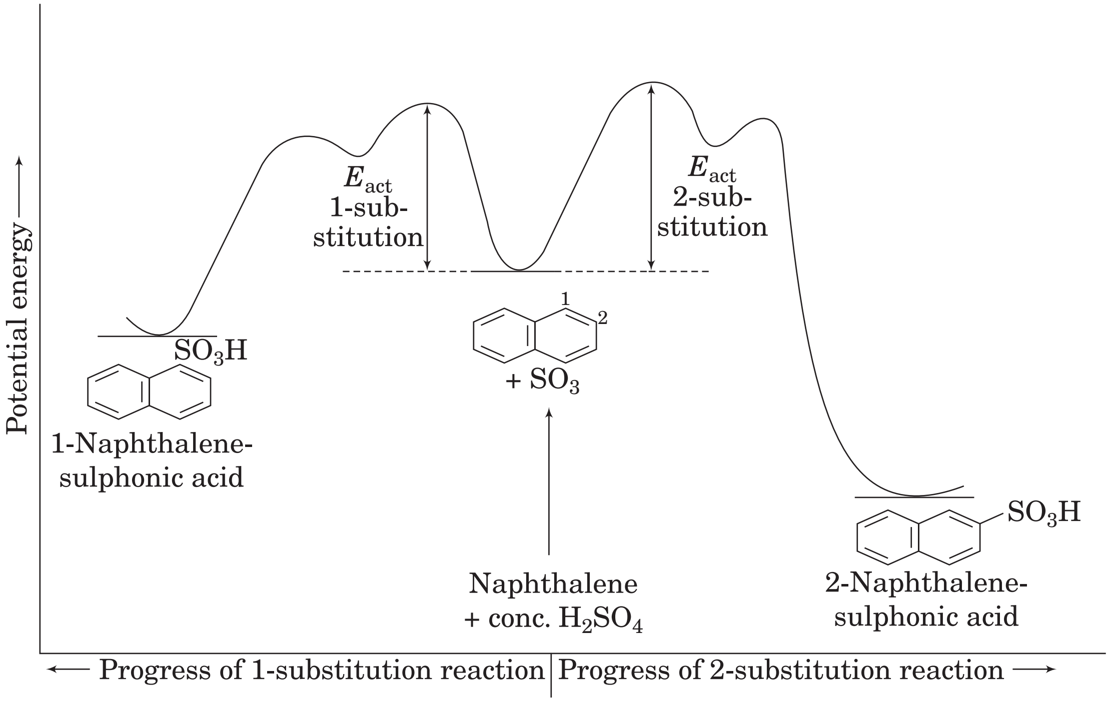
At 160°C, the main product is 2-naphthalenesulphonic acid. At this temperature, the reaction is reversible. Under this equilibrium conditions, the less stable but readily formed 1-acid undergoes ready desulphonation to yield naphthalene which then undergoes new attack at C-2 to yield the more stable 2-acid (the thermodynamic product). Because of greater activation energy, the 2-acid tends to resist desulphonation.



1-Naphthalene-sulphonic acid (formed rapidly and desulphonated rapidly) Naphthalene 2-Naphthalenesulphonic acid (formed slowly and desulphonated slowly)

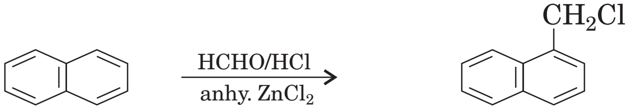
This reversibility is confirmed by the fact that 1-acid, when heated with concentrated H_2SO_4 at 160°C, produces the 2-acid predominantly.

The energy diagram for the sulphonation of naphthalene may be represented as follows:



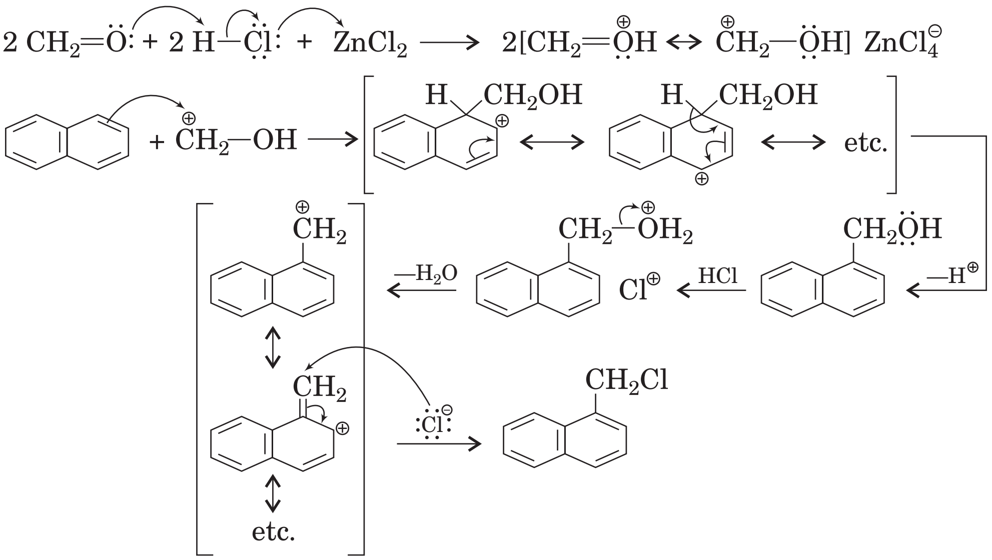
Potential energy
E_{act} 1-sub-stitution
E_{act} 2-sub-stitution
SO₃H
1-Naphthalene-sulphonic acid
1
2
+ SO₃
Naphthalene + conc. H₂SO₄
SO₃H
2-Naphthalene-sulphonic acid
← Progress of 1-substitution reaction
Progress of 2-substitution reaction →

(f) Chloromethylation Naphthalene undergoes chloromethylation (i.e., introduction of a —CH_2Cl group) when treated with formaldehyde and HCl in the presence of zinc chloride. 1-Isomer is obtained as the major product.

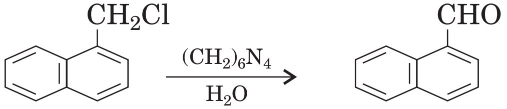


Naphthalene 1-Chloromethylnaphthalene

Mechanism of the reaction Protonation of formaldehyde by HCl in the presence of $ZnCl_2$ produces the hydroxymethyl cation $(\overset{\oplus}{C}H_2OH)$, the electrophilic species. This reacts with naphthalene to give 1-hydroxymethylnaphthalene which then reacts with HCl to yield 1-chloromethylnaphthalene.



When 1-chloromethylnaphthalene is treated with an aqueous solution of hexamethylenetetramine, 1-naphthaldehyde is obtained.



1-Naphthaldehyde

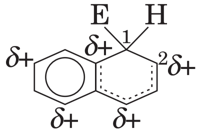
Rules for deciding which ring undergoes electrophilic substitution in substituted naphthalene ($C_{10}H_7G$) under kinetically controlled conditions:

Rule 1: When one ring contains a deactivating group G, further substitution occurs in the unsubstituted ring at an α- or 1-position.

Rule 2: When one ring contains an activating α-G, further substitution takes place in the same ring at 4-position, and to a smaller extent at 2-position. An activating β–G, on the other hand, produces only 1-substitution product.

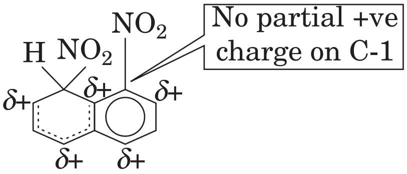
Rule 3: α- or 1-substitution always dominates.

Concept of alternant polarity as applied to the σ-complex for 1-attack on naphthalene by an electrophile ($E^{\oplus}$) and to use this concept to predict the major product from nitration of 1- and 2-nitronaphthalene at 0°C: When the electrophile ($E^{\oplus}$) forms a bond to a carbon atom of the aromatic ring, some positive charges are introduced on adjacent carbons and all other alternating carbons of the ring. This may be shown for 1-substitution of naphthalene:

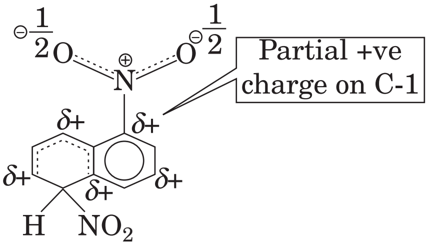


(Intermediate carbocation
or σ-complex involved in
1-substitution of naphthalene)

The —NO_2 group is a deactivating group. Therefore, further substitution occurs in the other ring at an α-position. 1-Nitronaphthalene undergoes nitration at 0°C to give 1,8-dinitronaphthalene as the major product. This is because attack by the electrophile $\overset{\oplus}{N}O_2$ at C-8 does not generate any positive charge on C-1 bonded to the —NO_2 group. 1,5-Dinitronaphthalene is obtained as the minor product because of steric strain in the C-8 position (*peri*-interaction) and also because attack by $\overset{\oplus}{N}O_2$ at C-5 generates a partial positive charge on C-1 bonded to —NO_2; this causes destabilization of the intermediate.

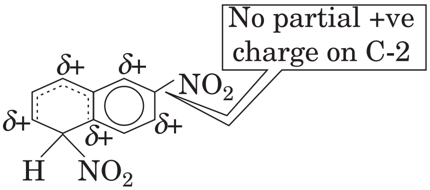


Carbocation intermediate
involved in 8-substitution
(more stable)

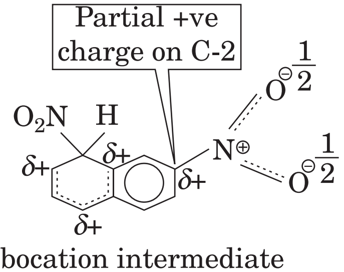


Carbocation intermediate
involved in 5-substitution
(less stable)

Due to the same basic reason, 1,6- and 1,7-dinitronaphthalene are obtained as the major and minor products, respectively, when 2-nitronaphthalene is subjected to nitration.



Carbocation intermediate
involved in 5-substitution
(more stable)

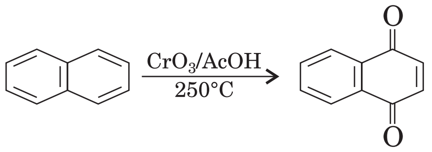


Carbocation intermediate
involved in 8-substitution
(less stable)

5.1.5.2 Oxidations

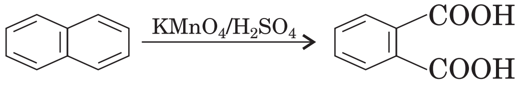
Oxidation of naphthalene by different oxidizing agents produces different products. For example:

(a)



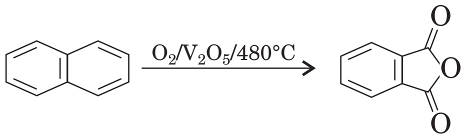
1,4-Naphthaquinone

(b)



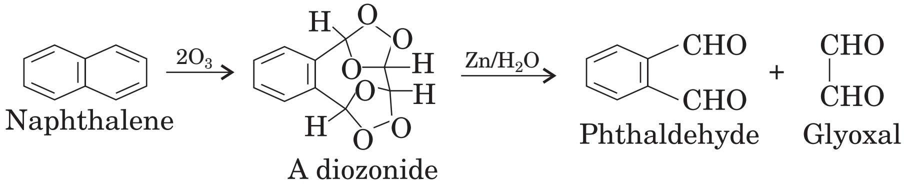
Phthalic acid

(c)



Phthalic anhydride

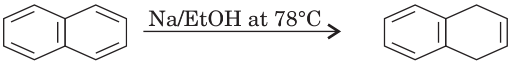
(d) **Ozonolysis of Naphthalene:** When treated with ozone naphthalene forms a diozonide and this, on treatment with Zn/H_2O, gives phthaldehyde and glyoxal.



5.1.5.3 Reductions

Naphthalene is reduced to varying degrees by different reducing agents. For example:

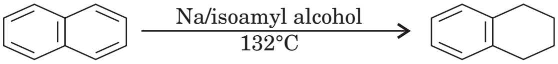
(a)



1,4-Dihydronaphthalene
or 1,4-Dialin

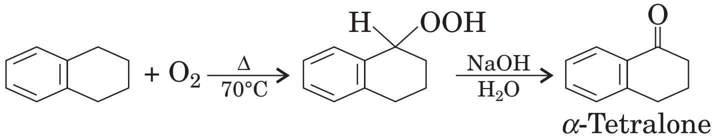
1,4-Dialin is unstable, readily isomerising to 1,2-dialin when heated with ethanolic sodium hydroxide.

(b)

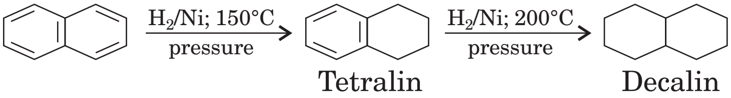


Tetralin

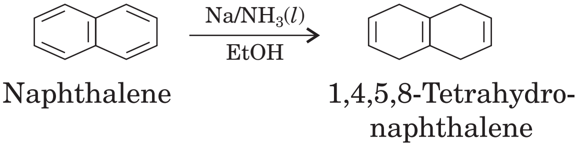
Heating tetralin in air for 50 h at 70°C and decomposing the peroxide so formed with aqueous NaOH produces α-tetralone.



(c) When naphthalene is catalytically reduced (under pressure) using nickel, tetraline and then *deca-hydronaphthalene* (*decalin*) are obtained:



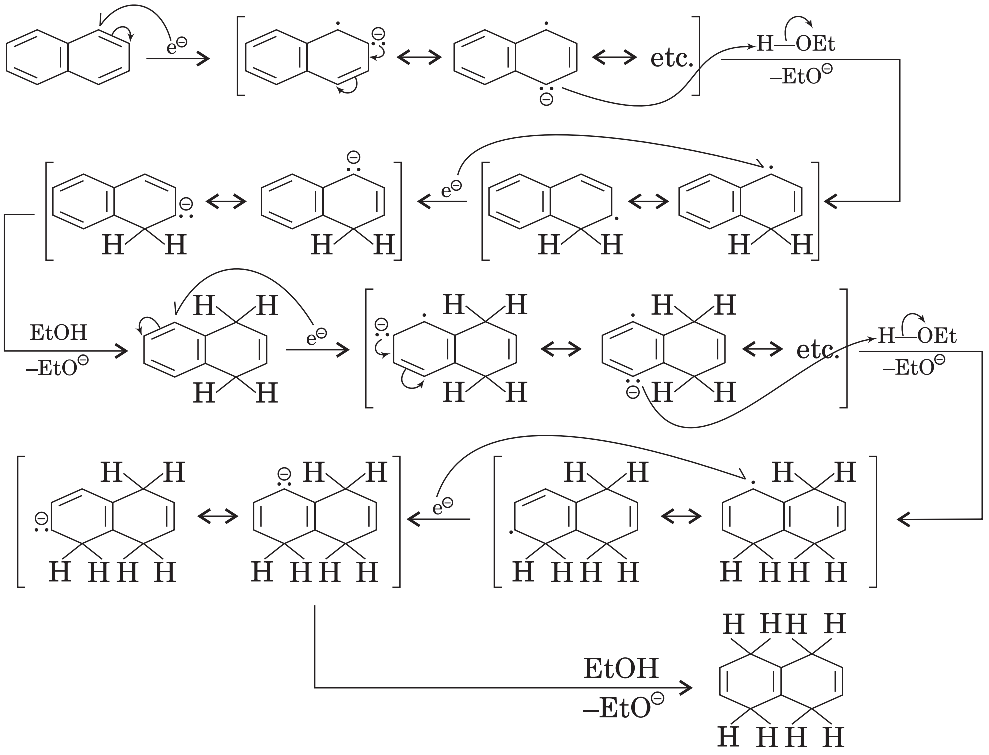
(d) **Birch reduction:** Naphthalene undergoes Birch reduction to give 1,4,5,8-tetrahydronaphthalene when treated with metallic sodium and liquid ammonia in the presence of ethanol.



Mechanism of the reaction The reaction proceeds through the steps as follows:

$$NH_3(l) + Na \rightleftharpoons \overset{\ominus}{e}(NH_3)_n + Na^{\oplus}$$

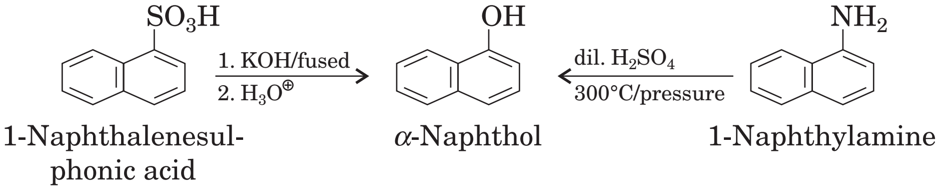
(solvated electron)



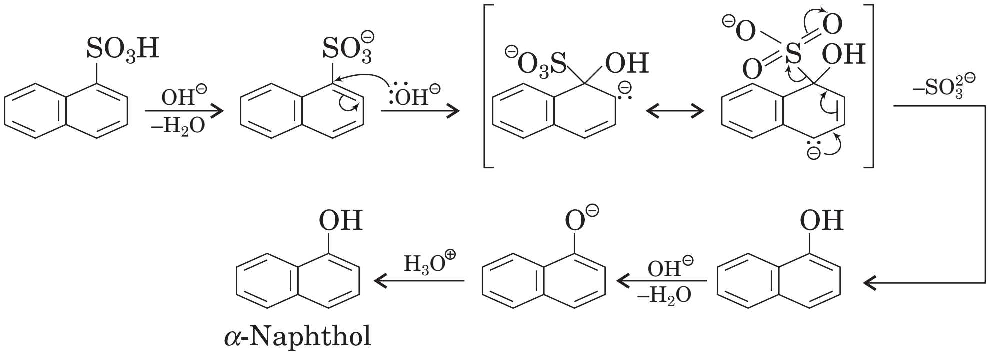
5.1.6 Derivatives of Naphthalene

5.1.6.1 Naphthols

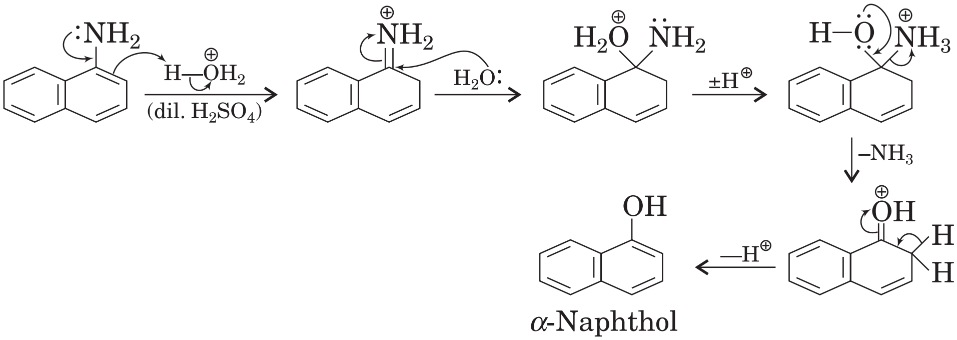
(i) Preparations Both α- and β-napthols occur in coal tar. However they are prepared by the alkali fusion of the corresponding sulphonic acid or by heating the corresponding amines with dilute H_2SO_4 under pressure. It is to be noted that aniline does not undergo the latter reaction.



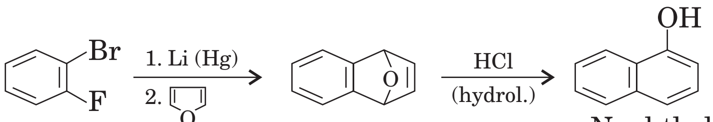
Mechanisms of the reactions Under vigorous conditions the sulphonate salt undergoes nucleophilic aromatic substitution (S_NAr) in which the $—SO_3^{\ominus}$ group is displaced by —OH.



Under vigorous conditions 1-naphthylamine undergoes hydrolysis to yield 1-naphthol as follows:

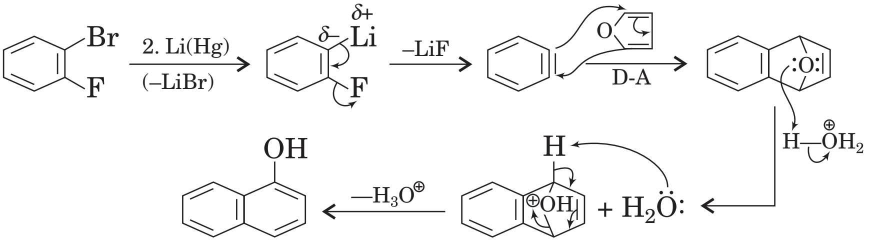


α-Naphthol can also be prepared by allowing *o*-bromofluorobenzene with lithium amalgam in the presence of furan followed by hydrolyzing the resulting cyclic ether with dilute hydrochloric acid.

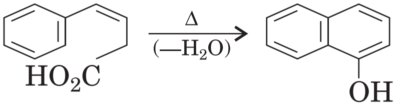


α-Naphthol

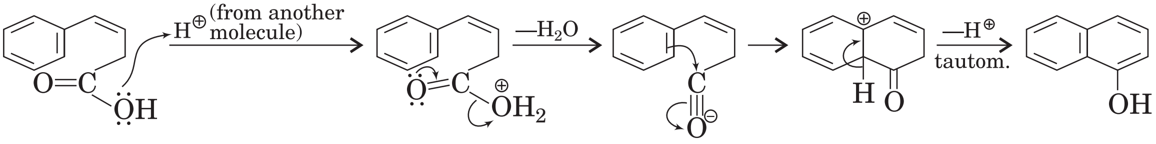
Mechanisms of the reactions *o*-Bromofluorobenzene reacts with lithium to form an aryllithium which eliminates LiF to yield the unstable intermediate benzyne. Benzyne then adds to furan (a Diels–Alder reaction) to give an adduct which on decomposition with hydrochloric acid gives α-naphthol.



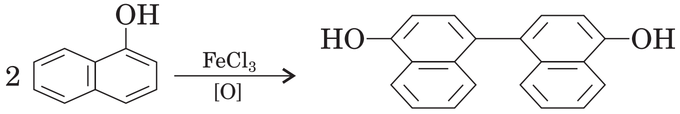
When phenylisocrotonic acid is heated, it cyclizes to yield α-naphthol.



Mechanism of the reaction This is a case of intramolecular acylation which takes place as follows:



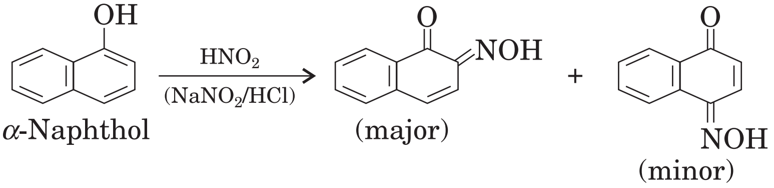
(ii) Properties Pure α-naphthol is a colourless solid having melting point 94°C. It dissolves in sodium hydroxide solution forming sodium α-naphthoxide. Unlike phenol it gives a violet-blue precipitate of α-binaphthol (4,4′-bis-1-naphthol) with ferric chloride solution.



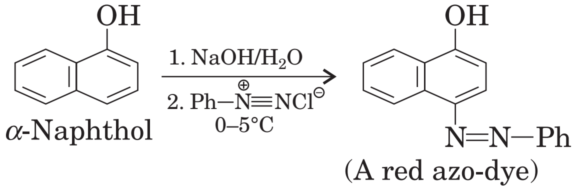
α-Naphthol

α-Binaphthol
(a violet-blue solid)

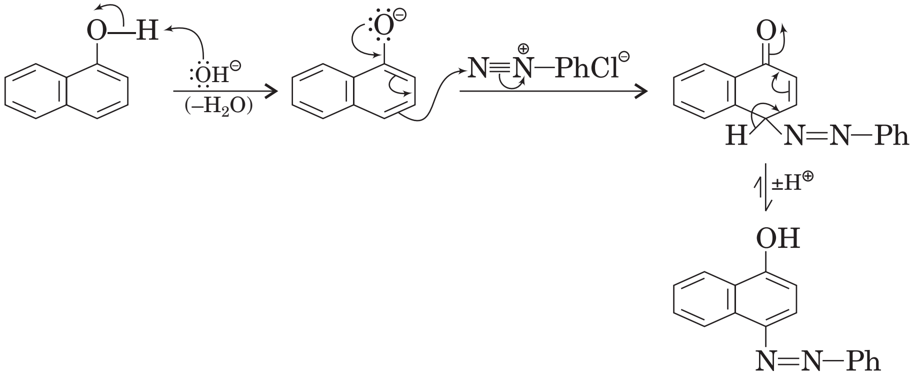
α-Naphthol reduces ammonical silver nitrate. It is oxidized by alkaline $KMnO_4$ to phthalonic acid and by chromic acid to α-naphthaquinone. It is reduced by metallic sodium and isopentanol to *ar*-tetrahydro-1-naphthol (*ar*-1-*tetralol*). When it is allowed to react with nitrous acid, a mixture of 2-oxime of β-naphthaquinone and 4-oxime of α-naphthaquinone is obtained with the former as the major product.



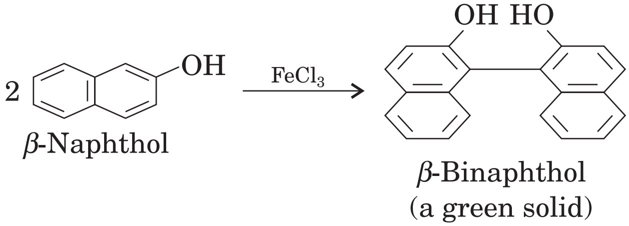
Alkaline solution of α-naphthol forms azo dyes by coupling with diazonium salts at the 4-position. For example:



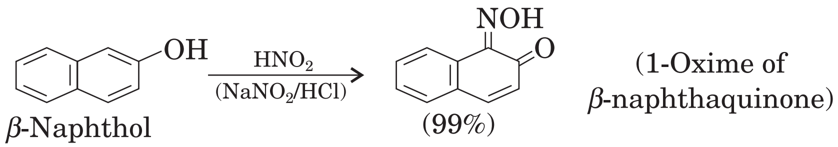
Mechanism of the reaction It is an electrophilic substitution reaction which takes place after formation of the naphthoxide salt as follows:



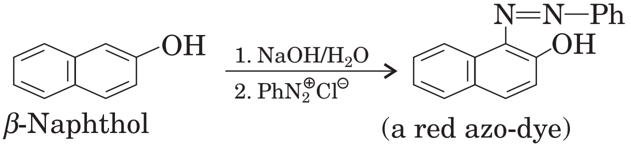
β-Naphthol, a colourless (or occasionally yellow) crystalline solid having melting point 120°C, resembles α-naphthol in most of its properties, but is more reactive. With ferric chloride it gives a green precipitate of β-binaphthol (1,1′-bis-2-naphthol).



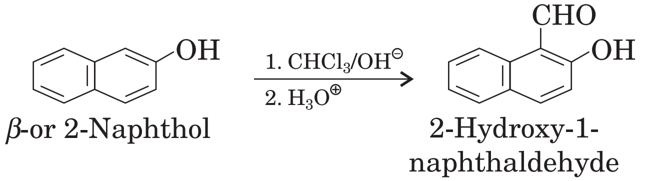
It reduces ammonical silver nitrate, and is oxidized by alkaline $KMnO_4$ to phthalonic acid. It is reduced by metallic sodium and isopentanol to mainly *ac*-tetrahydro-2-naphthol (*ac*-2-*tetralol*). It reacts with HNO_2 to form 1-oxime of β-naphthaquinone (nitroso-β-naphthol):



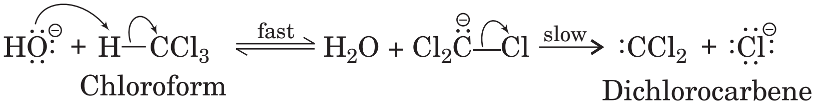
β-Naphthol couples with diazonium salts only in the adjacent α-position; if this position is already occupied, no coupling occurs. For example:

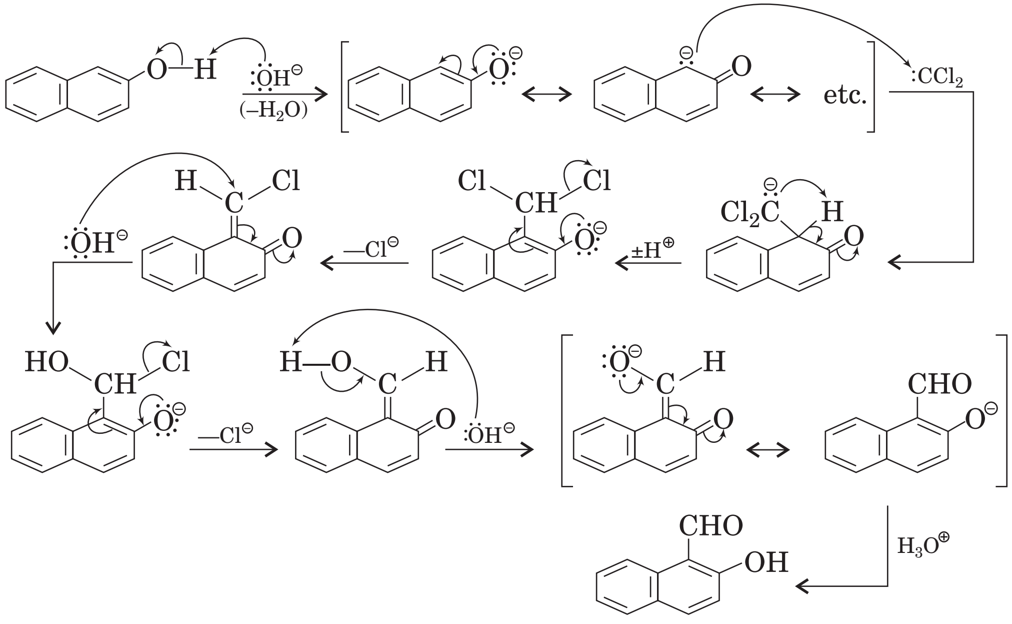


β-Naphthol undergoes the Reimer–Tiemann reaction to yield 2-hydroxy-1-naphthaldehyde when treated with a mixture of chloroform and alkali followed by acidification.



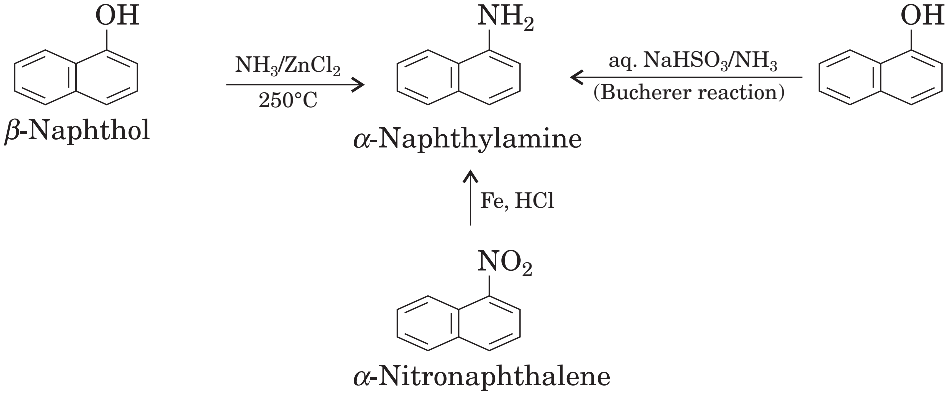
Mechanism of the reaction It is an electrophilic substitution reaction in which dichlorocarbene, obtained by the reaction of chloroform with alkali acts as the electrophile. Substitution occurs at 1-position.



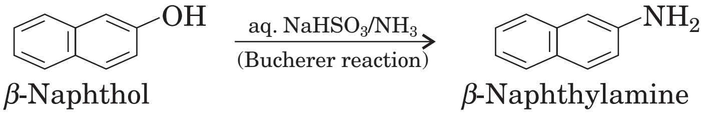


5.1.6.2 Naphthylamines

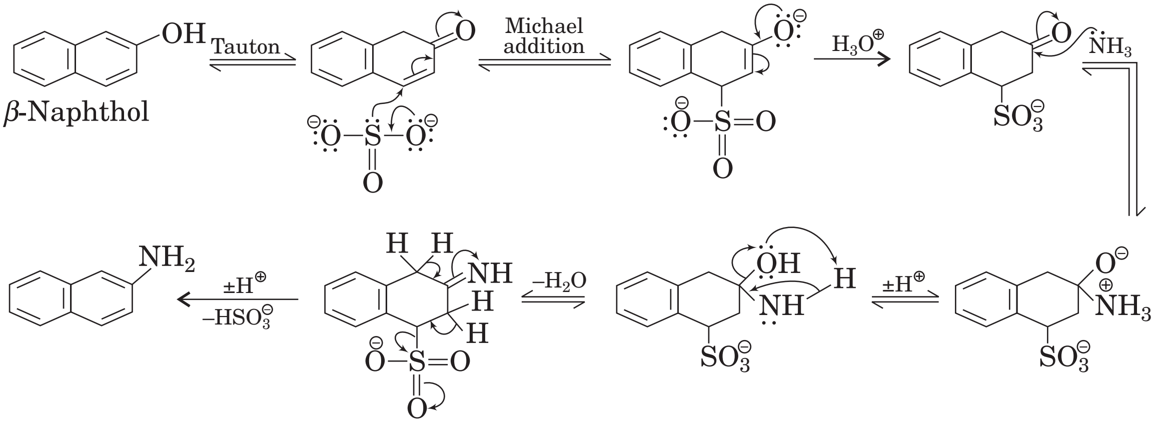
(i) Preparations α-Naphthylamine may be prepared by reducing α-nitronaphthalene with iron and hydrochloric acid (yield 80–85%). This method is, in fact, used industrially. It may also be prepared from α-naphthol by heating it with $ZnCl_2$ and ammonia at 250°C or by treating with aqueous sodium hydrogen sulphite and ammonia (the *Bucherer reaction*).



β-Naphthylamine is a very useful compound because most of the 2-substituted naphthalene derivatives are prepared from it. It is manufactured by heating β-naphthol with sodium hydrogen sulphite and ammonia.



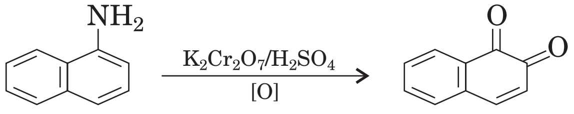
Mechanism of the reaction The mechanism of this reversible reaction involves the steps as follows: $HSO_3^{\ominus} + H_2O \rightleftharpoons H_3O^{\oplus} + SO_3^{2\ominus}$



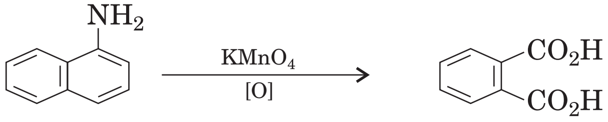
The keto-form of the naphthol and the imino-compound produced are stabilized by the addition of the sulphite ion.

β-Naphthylamine is prepared commercially in good yield (94–96%) by heating 2-naphthol with aqueous ammonium hydrogen sulphite at 150°C under pressure.

(ii) Properties α-Naphthylamine having melting point 50°C has an unpleasant odour. It turns red on exposure to air. It reduces ammonical silver nitrate and solutions of its salts form a blue precipitate with $FeCl_3$. When it is oxidized with boiling chromic acid and permanganate, α-naphthaquinone and phthalic are obtained, respectively.

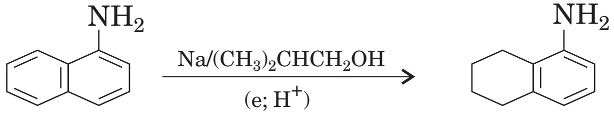


α-Naphthylamine α-Naphthaquinone



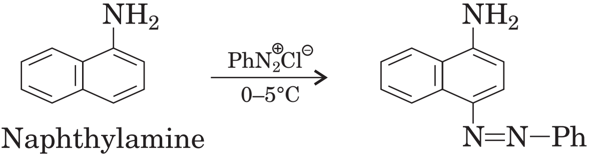
α-Naphthylamine Phthalic acid

α-Naphthylamine is reduced by sodium and isopentanol to *ar*-tetrahydro-1-naphthylamine (the prefix *ar*- is the abbreviation of *aromatic* and indicates that the four H-atoms are not in the ring containing the —NH_2 group.



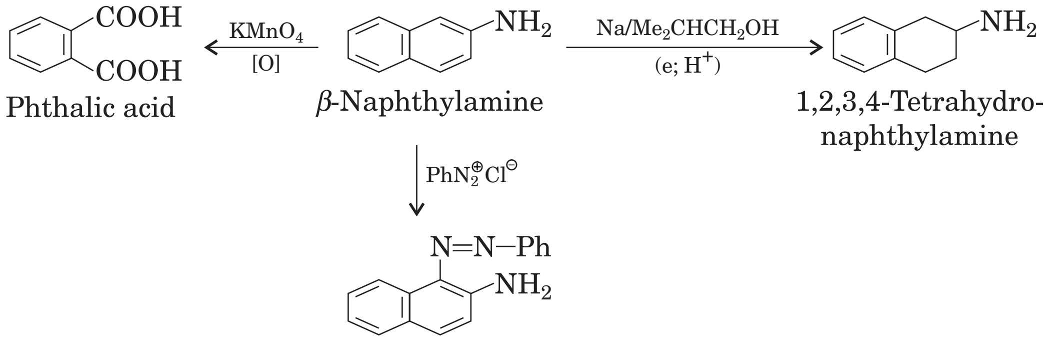
α-Naphthylamine *ar*-Tetrahydro-1-naphthylamine
or 5,6,7,8-tetrahydro-1-naphthylamine

1-Naphthylamine couples with diazonium salts in the 4-position.



α-Naphthylamine (An azo-dye)

β-Naphthylamine having melting point 112°C is a colourless compound. It reduces ammonical $AgNO_3$, but gives no colouration with $FeCl_3$. Like the α-isomer, it is oxidized to phthalic acid by permanganate. But with metallic sodium and isopentanol, it is reduced to 1,2,3,4-tetrahydro-naphthylamine. It couples with diazonium salts at 1-position; if it is occupied, no coupling takes place.



Phthalic acid

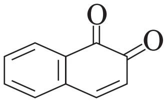
β-Naphthylamine

1,2,3,4-Tetrahydro-naphthylamine

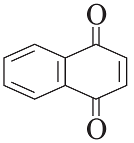
(An azo-dye)

5.1.6.3 Naphthaquinones

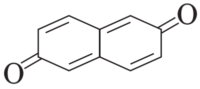
Although theoretically six naphthaquinones are possible (1,2-, 1,4-, 1,5-, 1,7-, 2,3- and 2,6-), only three are known (1,2-, 1,4- and 2,6-). However, derivatives of 2,3-naphthaquinone have been prepared.



1,2-Naphthaquinone
(β-Naphthaquinone)

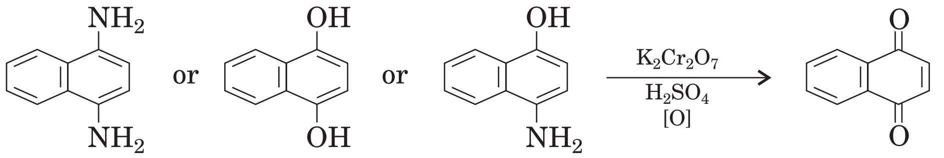


1,4-Naphthaquinone
(α-Naphthaquinone)



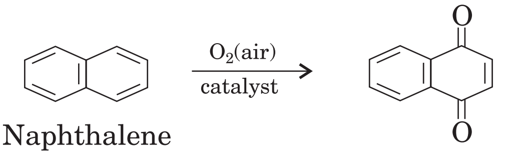
2,6-Naphthaquinone
(*Amphi*-naphthaquinone)

(i) Preparations 1,4-Naphthaquinone or α-naphthaquinone or 1,4-dihydronaphthalene-1,4-dione may be prepared by the oxidation of 1,4-diamino-, dihydroxy- or aminohydroxynaphthalene.



1,4-Naphthaquinone

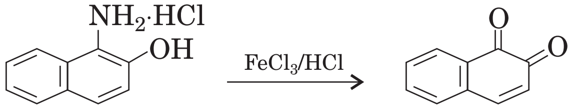
If may be also be prepared by the direct oxidation of naphthalene with $K_2Cr_2O_7/H_2SO_4$ or CrO_3/AcOH. It is commercially prepared by aerial oxidation of naphthalene in the presence of a suitable catalyst.



Naphthalene

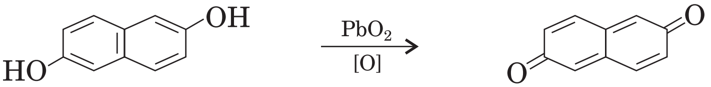
1,4-Naphthaquinone

1,2-Naphthaquinone or *β*-naphthaquinone or 1,2-dihydronaphthalene-1,2-dione may be prepared by oxidising 1-amino-2-naphthol hydrochloride with ferric chloride in hydrochloric acid (yield 93–94%).



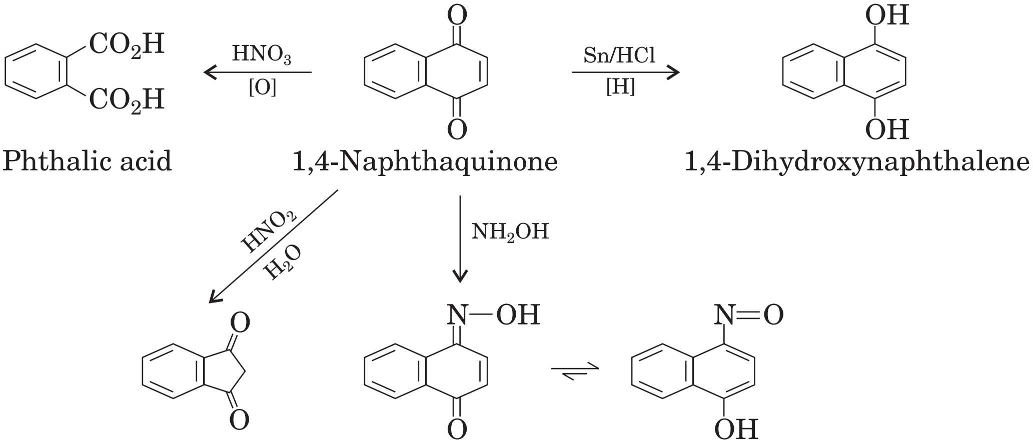
1-Amino-2-naphthol hydrochloride 1,2-Naphthaquinone

2,6-Naphthaquinone or *amphi*-naphthaquinone or 2,6-dihydronaphthalene-2,6-dione can be prepared by oxidising 2,6-dihydroxynaphthalene in benzene solution with 'active' lead oxide (prepared by decomposing lead tetraacetate with water).



2,6-Dihydroxynaphthalene 2,6-Naphthaquinone

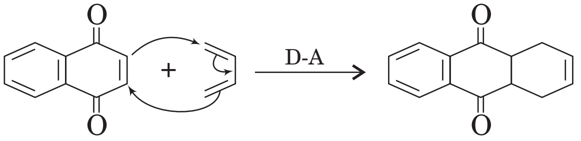
(ii) Properties 1,4-Naphthaquinone is a volatile yellow solid (m.p. 125°C) with a pronounced odour. Chemically it resembles *p*-benzoquinone in many ways, but it cannot be reduced by sulphurous acid. It is reduced by Sn/HCl to 1,4-dihydroxynaphthalene or naphthalene-1,4-diol and oxidised by nitric acid to phthalic acid. It reacts with hydroxyl amine to form a monoxime. In the solid state if exists as oxime, but in solution, the oxime form predominates in equilibrium with the nitrosophenol form. It can be converted to indane-1,3-dione (1,3-diketohydrindene) by treating with nitrous acid.



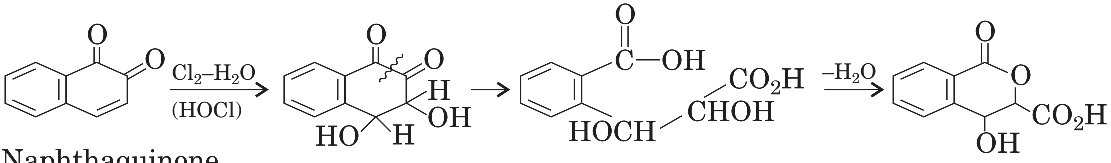
Phthalic acid 1,4-Naphthaquinone 1,4-Dihydroxynaphthalene

Indane-1,3-dione (predominates)

It undergoes the Diels–Alder reaction with butadiene to give an adduct.



1,2-Naphthaquinone is a non-volatile, odourless, red solid. It decomposes at 115–120°C. When it is treated with chlorine-water (or with hypochlorous acid), fission of the quinone ring with simultaneous hydroxylation occurs to yield phenylglyceric-*o*-carboxylic lactone.



1,2-Naphthaquinone

A lactone

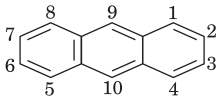
2,6-Naphthaquinone is an orange, non-volatile, odourless solid having melting point 135°C.

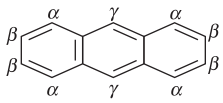
5.2 ANTHRACENE AND ITS DERIVATIVES

Anthracene, $C_{14}H_{10}$, having melting point 216°C, is a sublimable crystalline solid with blue fluorescence that forms a red picrate with picric acid. It is obtained from the anthracene oil fraction of coal-tar by cooling the latter and pressing the solid (that crystallises out) free from the liquid. The anthracene cake thus obtained is powdered and then washed successively with 'solvent naphtha' and pyridine to dissolve phenanthrene and carbazole respectively. Pure anthracene is then obtained by sublimation. Alternatively, after removal of phenanthrene, the remaining solid is fused with KOH, whereby potassio-carbazole is formed. The unreacted anthracene is then sublimed out of the melt and recovered.

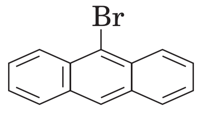
5.2.1 Nomenclature and Isomerism

Only ten carbon atoms in anthracene are either numbered or designated by Greek letters.

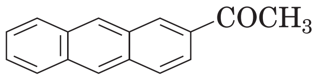




In this structure, 1,4,5, and 8 positions are equivalent, 2,3,6, and 7 positions are equivalent and 9 and 10 positions are equivalent, i.e., there are three non-equivalent positions in the molecule. Hence, three isomeric mono substituted anthracene derivatives are possible. In the case of disubstituted derivatives, 15 isomers are possible when both substituents are the same.



9-Bromoanthracene

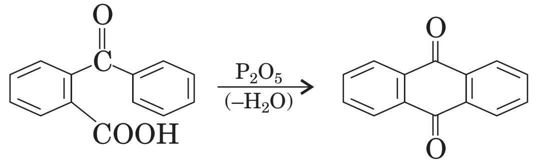


1-Acetylanthracene

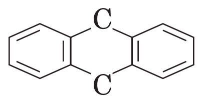
5.2.2 Structure of Anthracene

The structure of anthracene has been established from the following facts and conclusions therefrom.

1. Elemental analysis and molecular weight determination of anthracene show that its molecular formula is $C_{14}H_{10}$.
2. It exhibits the properties of both aromatic and unsaturated compounds. Thus, one mole of it adds one mole of Br_2, Cl_2 and H_2 and two moles of metallic sodium. It undergoes sulphonation directly treated with conc. H_2SO_4.
3. Fourteen H-atoms are required for its complete hydrogenation in the presence of Ni catalyst. The molecular formula of the resulting compound is $C_{14}H_{24}$. The molecular formula of an open-chain saturated hydrocarbon consisting of 14 C-atoms is $C_{14}H_{30}$. If these two molecular formulas are compared, we see that the completely hydrogenated product of anthracene contains 6 H atoms less than the corresponding open-chain hydrocarbon. This suggests that anthracene contains seven π-bonds in a three-ring system.
4. When anthracene is oxidized with chromic acid ($Na_2Cr_2O_7$ plus H_2SO_4), anthraquinone ($C_{14}H_8O_2$) is obtained; this on Zn dust distillation gives back anthracene. This observation indicates than on oxidation anthracene retains its cyclic structure and anthraquinone is a derivative of anthracene. Therefore, if the structure of anthraquinone can be established, the carbon skeleton of anthraquinone will be known and then the carbon skeleton of anthracene will also be known. When *o*-benzoylbenzoic acid is treated with phosphorus pentoxide, anthraquinone is obtained. The structure of anthraquinone has, therefore, been established.



o-Benzoylbenzoic acid Anthraquinone

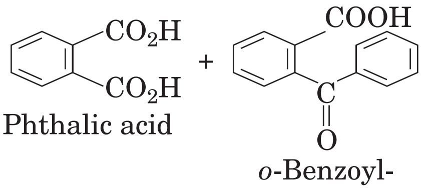


I

Hence, it becomes clear that anthraquinone contains the carbon skeleton I. Therefore, anthracene also contains the carbon skeleton I.

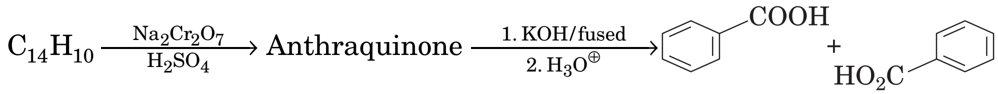
5. The following degradation reactions also supports the presence of the carbon skeleton I in anthracene.

(a) $C_{14}H_{10} \xrightarrow{Br_2} C_{14}H_9Br \xrightarrow[2.\ H_3O^{\oplus}]{1.\ KOH/fused} C_{14}H_9OH \xrightarrow{[O]}$

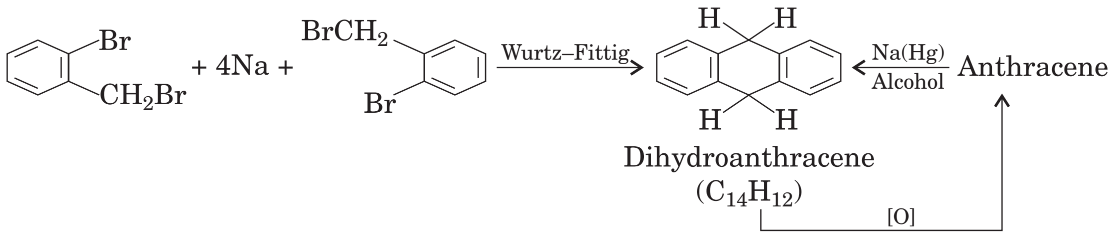


Phthalic acid

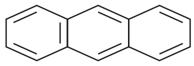
o-Benzoyl-
benzoic acid

(b) 

6. The presence of the carbon skeleton I in anthracene has also been established by the fact that when two moles of *o*-bromobenzyl bromide is allowed to react with metallic sodium, a dihydroanthracene is obtained which is identical with that obtained on reduction of anthracene by Na(Hg)/alcohol. Dihydroanthracene on mild oxidation produces anthracene.

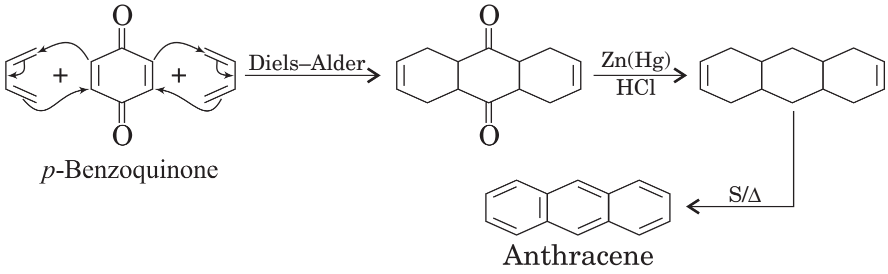


Considering all these facts anthracene can be represented as a linear combination of three benzene rings in which the terminal rings are fused at *o*-positions of the middle ring as represented below (A).



A

The structure of anthracene has been confirmed by a number of syntheses. For example, it can be prepared from *p*-benzoquinone and butadiene as follows:



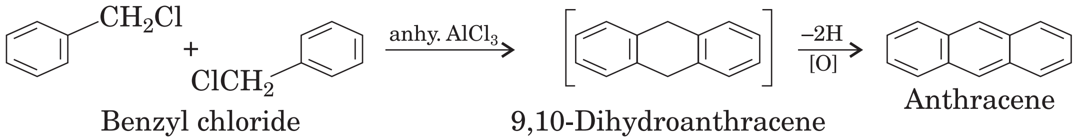
5.2.3 Synthesis of Anthracene

Anthracene can be synthesized by the methods such as follows:

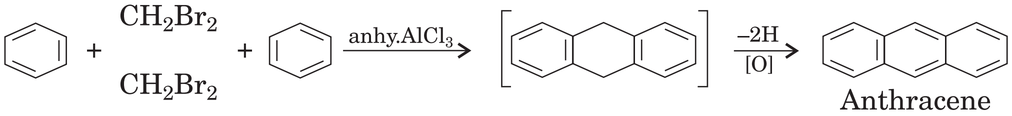
5.2.3.1 Friedel–Crafts Alkylation

Synthesis of anthracene may be carried out by this reaction using three different substrates:

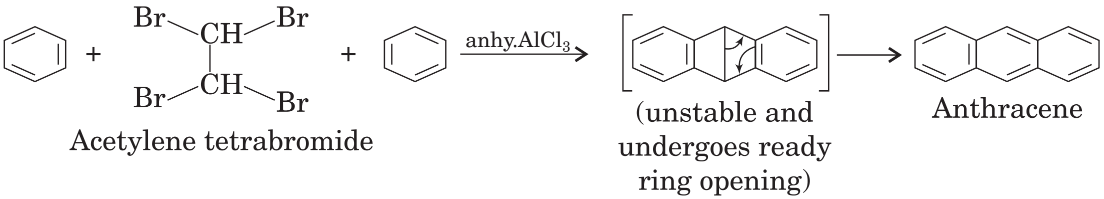
(i) Friedel-Crafts alkylation between two benzyl chloride molecules produces 9,10-dihydroanthracene which readily eliminates two H-atoms under the reaction condition to yield anthracene.



(ii) Friedel–Crafts alkylation of benzene with methylene dibromide (CH_2Br_2) also produces anthracene.

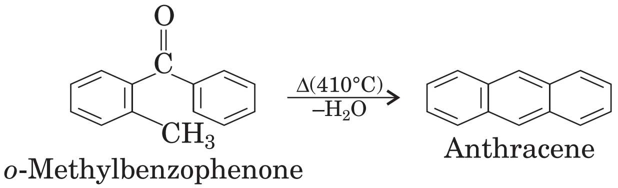


(iii) Anthracene is also obtained when Friedel–Crafts alkylation of benzene is carried out with acetylene tetrabromide.



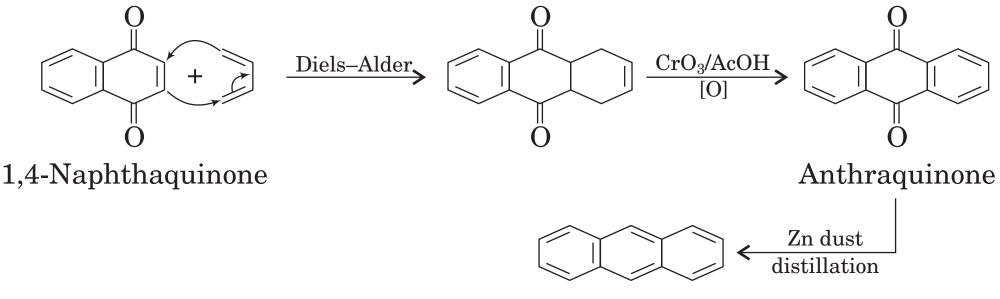
5.2.3.2 Elbs Reaction

The Elbs reaction involves pyrolysis of a diaryl ketone containing a methyl or methylene group *ortho* to the carbonyl group. For example, *o*-methylbenzophenone produces anthracene when heated at 410°C.

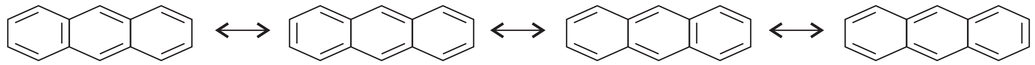


5.2.3.3 Diels–Alder Reaction

The Diels–Alder reaction between 1,4-naphthaquinone and butadiene followed by oxidation of the product with CrO_3 in glacial acetic acid leads to the formation of anthraquinone. This, on distillation with zinc dust, produces anthracene.



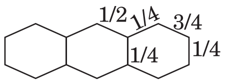
Position of the double bond in anthracene Anthracene is best regarded as a resonance hybrid of four resonance structures:



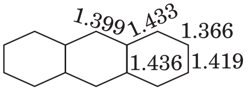
I II III IV

Among these four resonance structures (I) and (III) are more contributing because they contain the maximum number of benzenoid rings (Fries rule).

Assuming equal contribution of each of the canonicals the double bond character of the various bonds and the bond lengths in Å units (as determined by X-ray diffraction method) are shown in the following structures (V) and (VI), respectively.



(V)



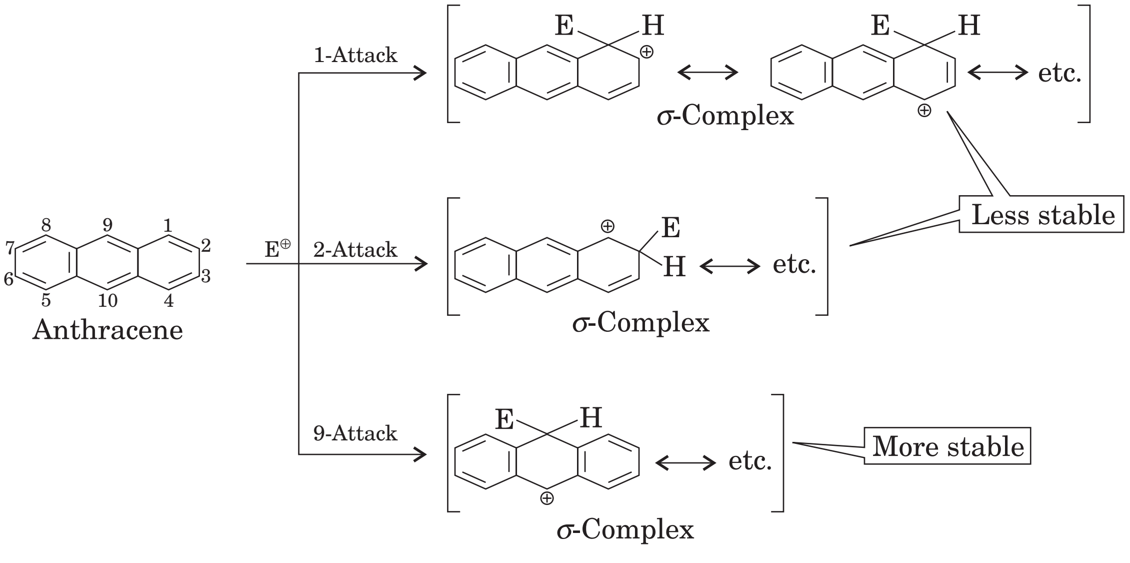
(VI)

5.2.4 Reactions of Anthracene

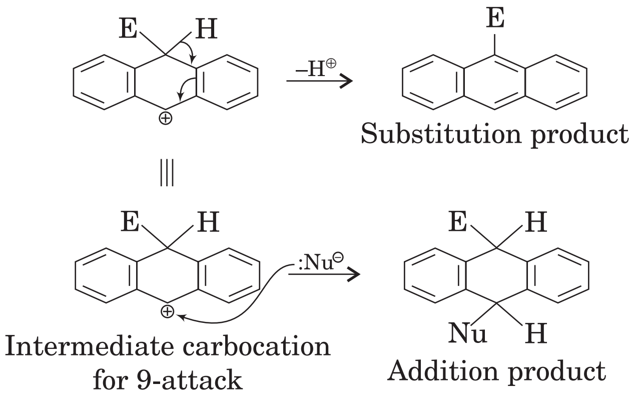
Resonance energy of anthracene is 84 kcal/mol (351.3 kJ/mol). The value is much less than the combined resonance energy of three benzene rings (3 × 36 = 108 kcal/mol). Therefore, anthracene is less stable than benzene and consequently more reactive.

Reactions

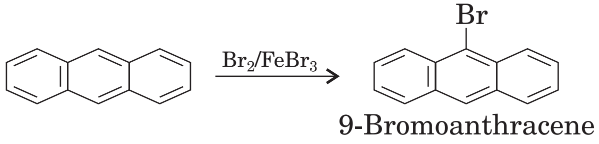
(a) Electrophilic substitution and addition reactions When anthracene is subjected to an electrophilic substitution reaction, it produces preferably 9- or 9,10-disubstituted product or 9,10-addition product. The reason for preferential substitution or addition at 9,10-positions can be easily understood by considering the stabilities of the intermediate carbocations or σ-complexes for attack at 1-, 2- and 9-positions (only these positions are non-equivalent).



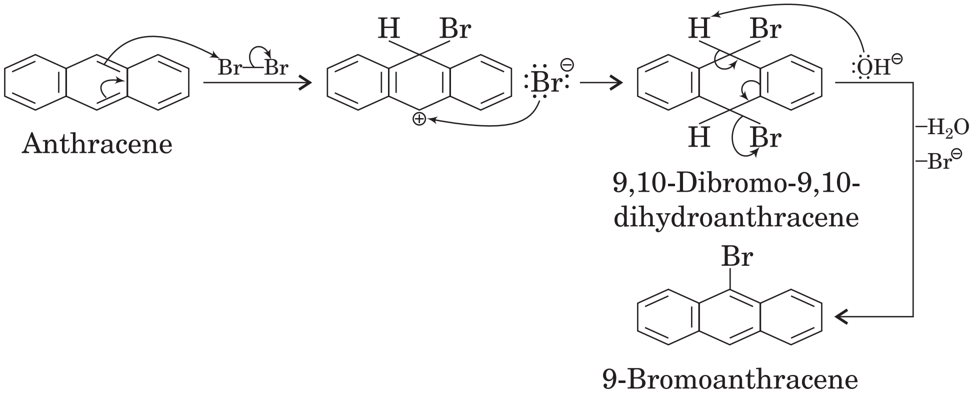
The electrophilic attack at C-1 or C-2 leads to an intermediate carbocation or σ-complex that contains a naphthalene system, whereas the attack at C-9 gives an intermediate carbocation in which there are two benzene rings. Since the resonance energy of the two benzene rings (2 × 36 = 72 kcal/mol) exceeds that of one naphthalene moiety (61 kcal/mol), the intermediate carbocation for attack at C-9 is most stable among the three. The reaction, therefore, takes places preferably through this most stable intermediate which subsequently loses a proton to yield the 9-substituted product or adds a nucleophile to give the 9,10-addition product.



(i) Halogenation Bromination of anthracene takes place at the 9-position to give 9-bromoanthracene.

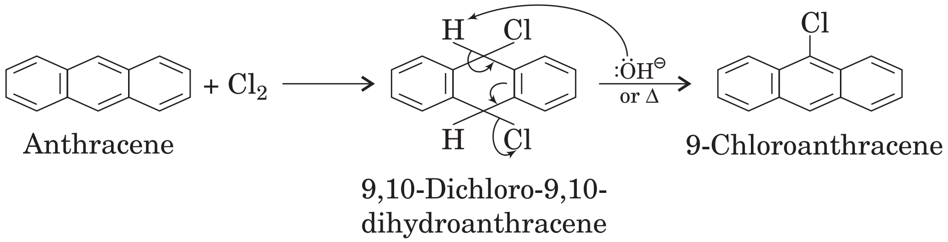


There is also a tendency for simultaneous addition of bromine to take place at 9- and 10-positions. The resulting addition product, when treated with base eliminates a molecule of HBr to yield 9-bromoanthracene.



Bromination of anthracene in boiling CCl_4 solution gives 9,10-dibromoanthracene (83–88% yield)

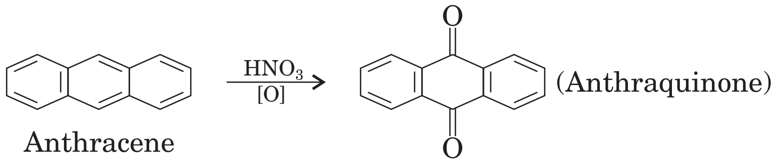
When chlorine is passed in a cold solution of anthracene in carbon tetrachloride and the resulting 9,10-dichloro-9,10-dihydroanthracene is heated or treated with alkali, 9-chloroanthracene is obtained.

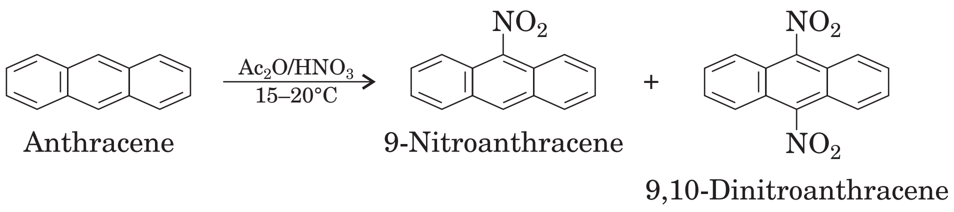


Sulphuryl chloride, at room temperature, converts it into 9,10-dichloroanthracene.

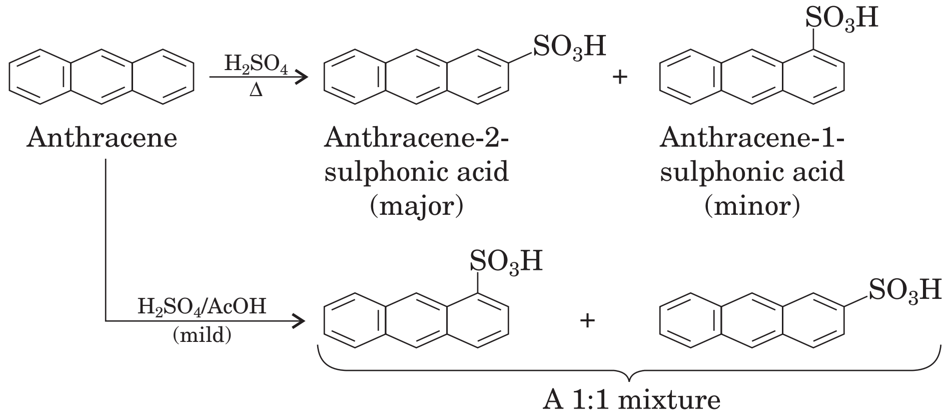
The best method of preparing 9-chloro- or 9-bromoanthracene is to heat anthracene with the corresponding cupric halide in carbon tetrachloride solution (98–99% yield).

(ii) Nitration Attempts to nitrate anthracene with aqueous HNO_3 lead to the formation of anthraquinone by oxidation. However, when the nitration is carried out in acetic anhydride at 15–20°C, 9-nitroanthracene and 9,10-dinitroanthracene are obtained. At 294°C it gives 9,10-dinitro derivative predominantly.

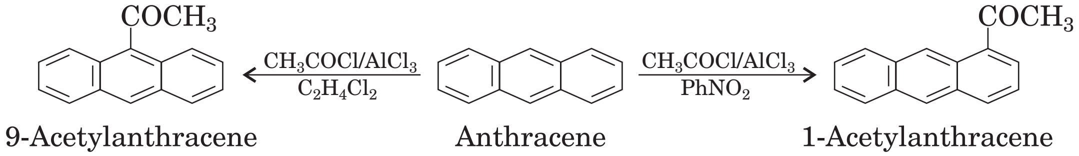




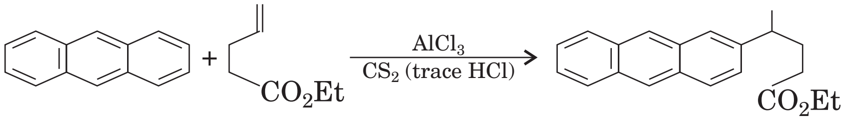
(iii) Sulphonation When sulphonation of naphthalene is carried out at high temperature, the 2-sulphonic acid is obtained predominantly. However, when sulphonation is carried out in glacial acetic acid under milder conditions, a 1:1 mixture of 1- and 2-isomers is obtained. Unlike naphthalene-1-sulphonic acid, the 1-isomer does not rearrange to give the 2-isomer at higher temperature.



(iv) Friedel–Crafts reaction Friedel–Crafts acylation of anthracene with acetyl chloride in nitrobenzene as solvent produces 1-acetyl derivative as the major product. However, the major product in ethylene dichloride is 9-acetyl derivative.

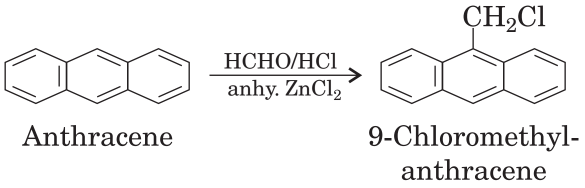


Friedel-Crafts alkylation of anthracene with bulky alkylating agents such as ethyl allylacetate in CS_2 as solvent at 0–20°C gives the 2-substituted anthracene as the major product.

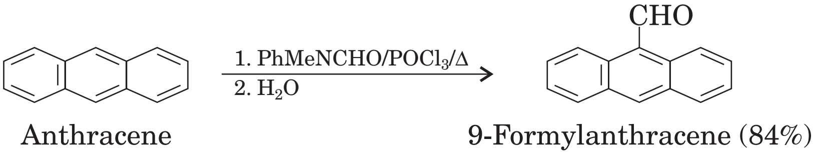


The preference of 2-position over 1- and 9-positions is attributed to the steric hindrance between the approaching bulky reagent and the *peri*-hydrogen.

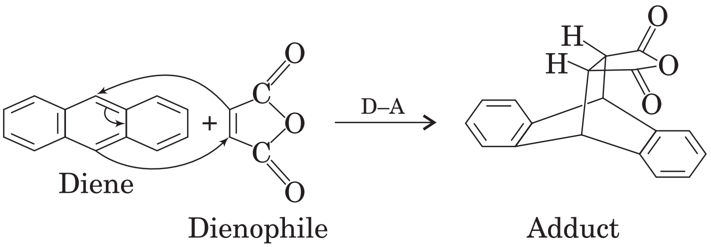
(v) Chloromethylation Anthracene undergoes chloromethylation when treated with formaldehyde and HCl in the presence of zinc chloride to give 9-chloromethyl anthracene.



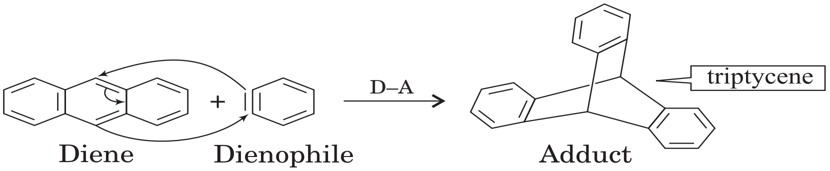
(vi) Vilsmeier–Haak formylation Anthracene undergoes formylation at C-1 when treated with PhNMeCHO in the presence of phosphorus oxychloride ($POCl_3$) followed by treating the resulting iminium ion with water.



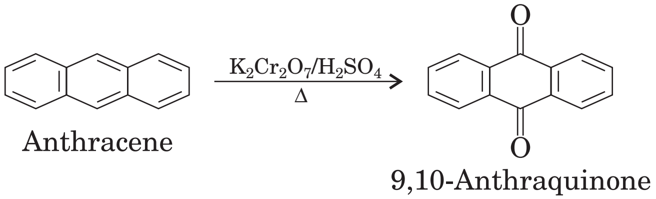
(b) Diels–Alder reaction Anthracene undergoes the Diels–Alder reaction in the 9,10-positions to form *endo*-anthracene anhydride.



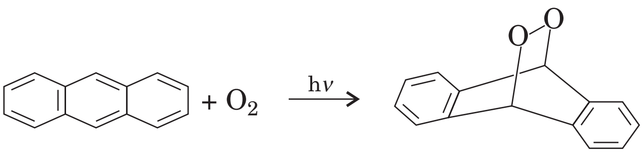
It also reacts with benzyne to form triptycene.



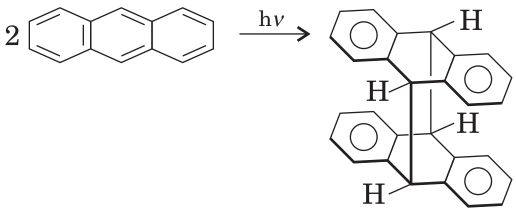
(c) Oxidation It is less resistant towards oxidation than naphthalene and readily forms 9,10-anthraquinone when oxidized with potassium dichromate in H_2SO_4.



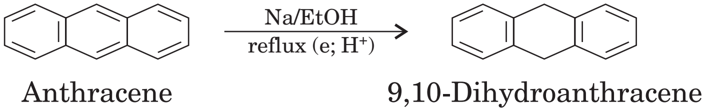
Anthracene undergoes peroxidation, i.e., addition of a molecule of O_2 to form a 9,10-peroxide in low yield in the presence of light.



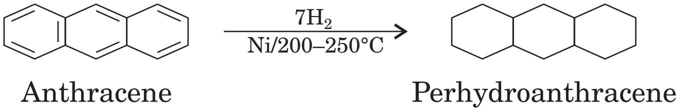
Anthracene forms a dimer when its solution in xylene is exposed to light.



(d) Reduction Sodium and ethanol reduces anthracene to 9, 10-dihydroanthracene.



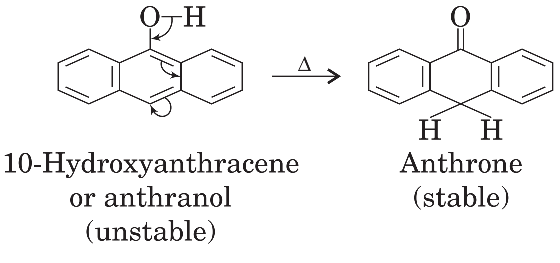
Catalytic reduction of anthracene using nickel at 200–250°C gives, according to the amount of hydrogen used, tetra-, hexa- and oxtahydroanthracene, and finally perhydroanthracene ($C_{14}H_{24}$).



5.2.5 Derivatives of Anthracene

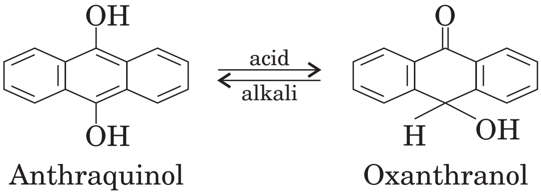
5.2.5.1 Hydroxyanthracenes

1- and 2-hydroxyanthracenes, known as 1- and 2-anthrols are obtained by fusing the corresponding sulphonic acids with alkali. 10-Hydroxyanthracene having melting point 120°C is an unstable compound and readily tautomerizes to give stable anthrone (m.p. 154°C).



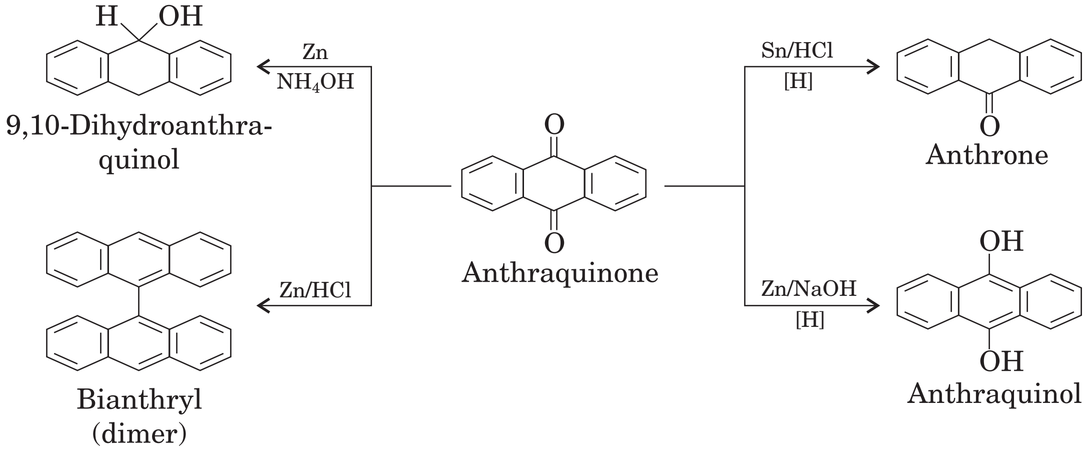
(In anthrone or 10-keto-9,10-dihydroanthracene, the keto-group is numbered last and consequently its enol tautomer is known as 10- and not 9-hydroxyanthracene.)

Anthracene-9,10-diol or anthraquinol or anthrahydroquinone is a brown solid having melting point 180°C. Its alkaline solution (deep red) undergoes oxidation in air to give anthraquinone. When anthraquinol in alkaline solution is immediately acidified, it partly tutomerizes to oxanthranol (m.p. 167°C).



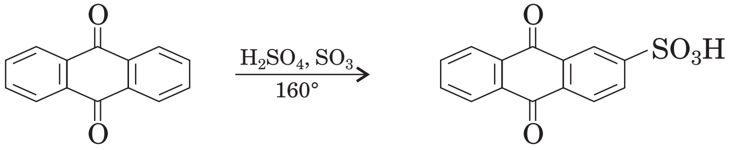
5.2.5.2 Anthraquinones

Out of nine possible isomeric anthraquinones only three are known and these are 1,2-, 1,4- and 9,10-anthraquinones. The last one is commonly known as anthraquinone. It is a pale yellow solid having melting point 280°C. It is quite stable and sublimes as needles. It produces various reduction products depending upon the reducing agent used.



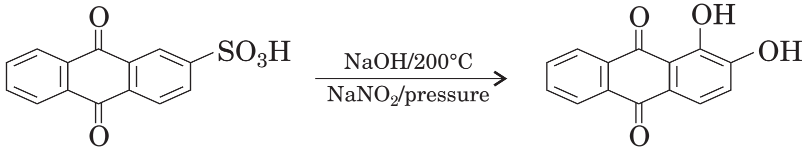
Anthraquinone, the most important derivative of anthracene in view of its wide applications in dye industry can be prepared by oxidizing anthracene with $Na_2Cr_2O_7$ and H_2SO_4. It can be prepared commercially by catalytic oxidation of anthracene or the Friedel–Crafts reaction involving phthalic anhydride and benzene.

Anthraquinone is readily sulphonated with fuming H_2SO_4 (oleum) at 160°C to give 2-sulphonic acid as the major product. However, the 1-isomer is the major product when mercuric sulphate is used as a catalyst. Anthraquinone-2-sulphonic acid is largely used in the manufacture of anthraquinone dyes.



Anthraquinone Anthraquinone-2-sulphonic acid

Alizarin (1,2-dihydroxyanthraquinone), an anthraquinone mordant dye can be synthesized by fusing anthraquinone-2-sulphonic acid with NaOH in the presence of sodium nitrite ($NaNO_2$) or potassium chlorate ($KClO_3$) in an autoclave at 200°C.



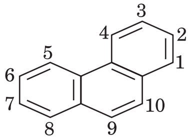
Anthraquinone-2-sulphonic acid Alizarin (a dye)

5.3 PHENANTHRENE AND ITS DERIVATIVES

Phenanthrene ($C_{14}H_{10}$) is isomeric with anthracene. In phenanthrene the three benzene rings are angularly fused. It occurs in the anthracene oil fraction of coal-tar, and is separated from anthracene by washing with solvent naphtha which dissolves phenanthrene. It is a solid having melting point 99°C and gives blue fluorescence. With picric acid it forms a picrate.

5.3.1 Nomenclature and Isomerism

The ring carbons in phenanthrene are numbered as shown below:



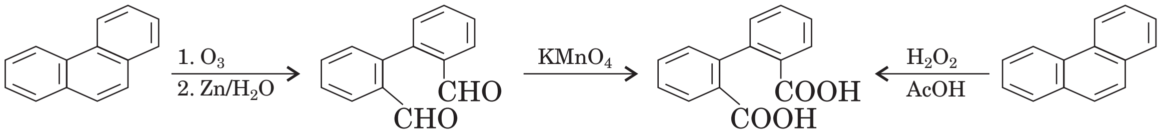
There are five monosubstituted derivatives of phenanthrene because there are five non-equivalent positions. Twenty five disubstituted products are possible if the two substituents are identical.

5.3.2 Structure of Phenanthrene

The structure of phenanthrene has been established from the following facts and conclusions therefrom:

1. Elemental analysis and molecular weight determination suggest that the molecular formula of phenanthrene is $C_{14}H_{10}$.

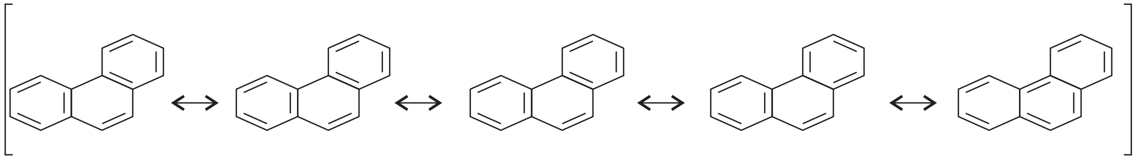
2. Phenanthrene has seven double bonds as it consumes seven molecules of hydrogen to yield perhydrophenanthrene on catalytic hydrogenation.
3. Ozonolysis (followed by oxidation) or oxidation with peracetic acid produces diphenic acid. This observation suggests that the three benzene rings in phenanthrene are angularly fused.



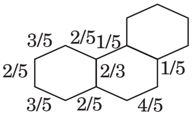
Diphenic acid

Therefore, the structure of phenanthrene is that as shown above.

Positions of the double bonds in phenanthrene Phenanthrene may be represented as a hybrid of the following five resonance structures.



Its resonance energy is 387.0 kJ/mol or 92.5 kcal/mol. The partial double-bond character of the various bonds in phenanthrene is shown in the following structure.

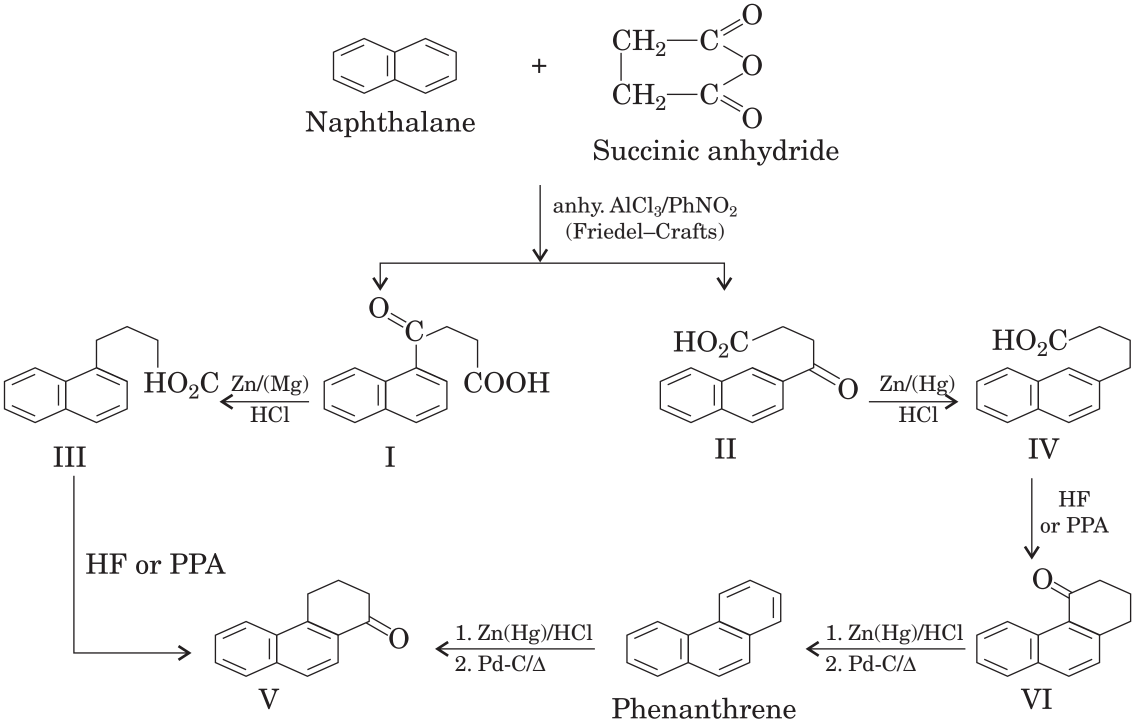


5.3.3 Synthesis of Phenanthrene and Its Derivatives

The five important methods for the synthesis of phenanthrene are as follows:

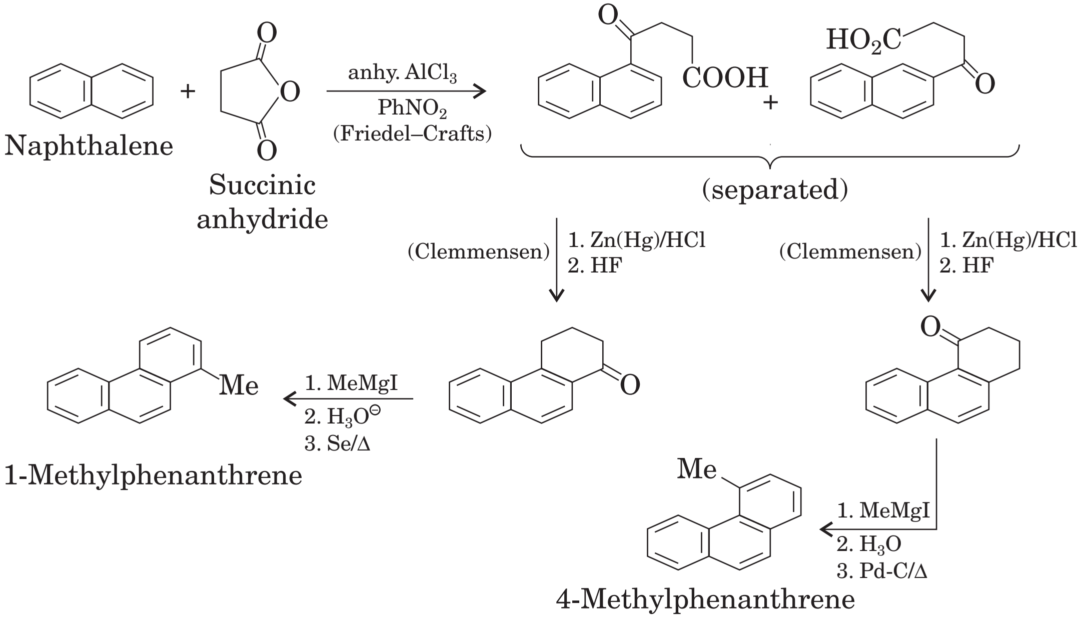
5.3.3.1 Haworth Method

Succinoylation of naphthalene produces two isomeric keto acids. These are β-(1-naphthoyl)propionic acid (I) and β-(2-naphthoyl)propionic acid (II). These two isomers can be readily separated. Clemmensen reduction affords γ-(1-naphthyl)butyric acid (III) and γ-(2-naphthyl)butyric acid (IV), respectively. Acid-catalyzed cyclization produces 1-keto-1,2,3,4-tetrahydronaphthalene (V) and 4-keto-1,2,3,4-tetrahydronaphthalene (VI). Clemmensen reduction followed by aromatization (by heating with palladized charcoal) of either isomer produces phenanthrene.

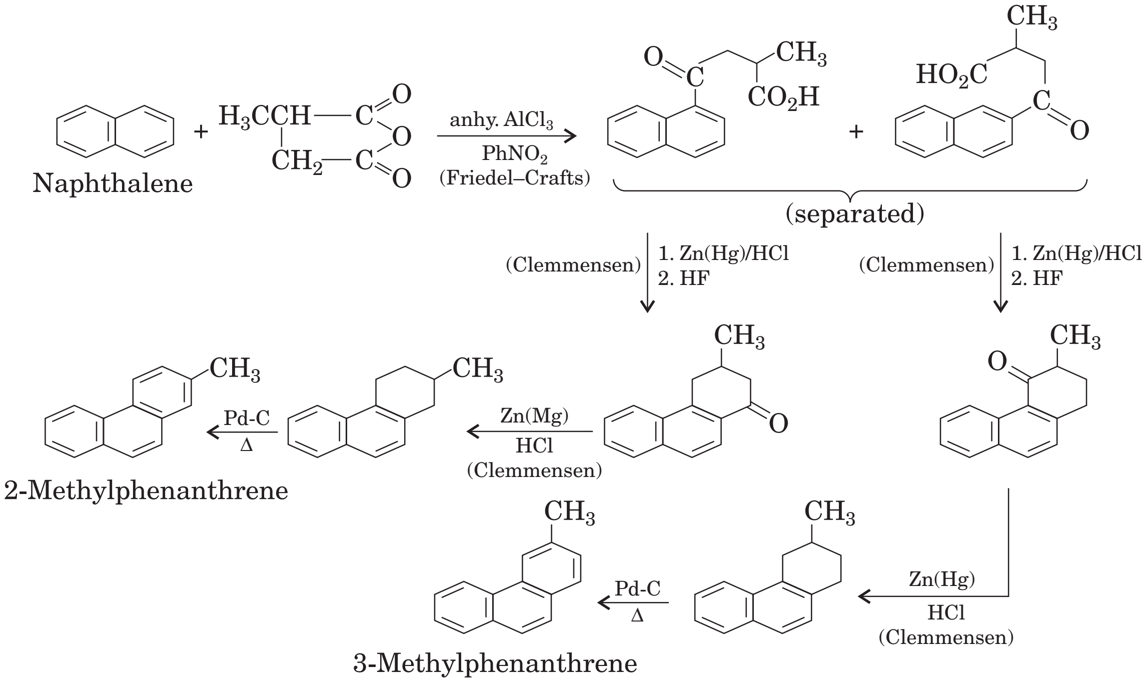


Since there are five non-equivalent positions (1,2,3,4 and 9) in phenanthrene, five methylphenanthrenes are possible. Synthesis of these compounds based on Haworth method are outlined below:

1 and 4-methylphenanthrenes

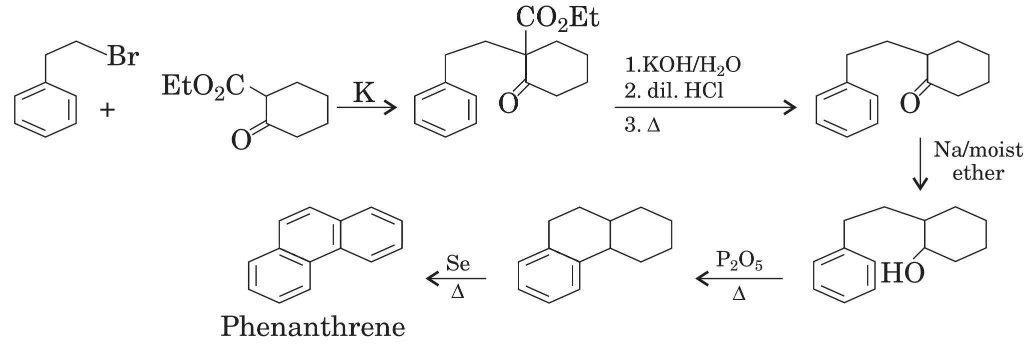


2 and 3-methylphenanthrene



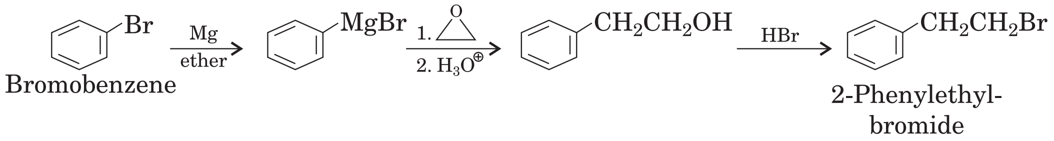
5.3.3.2 Bardhan–Sengupta Method

This method involves (i) treatment of ethyl cyclohexanone-2-carboxylate (a β-keto ester) with 2-phenylethyl bromide in the presence of potassium followed by hydrolysis and decarboxylation to yield a ketone, (ii) reduction of the resulting ketone to form the corresponding alcohol and (iii) acid-catalyzed cyclization of the resulting alcohol (after dehydration) followed by aromatization by heating with selenium to yield phenanthrene.

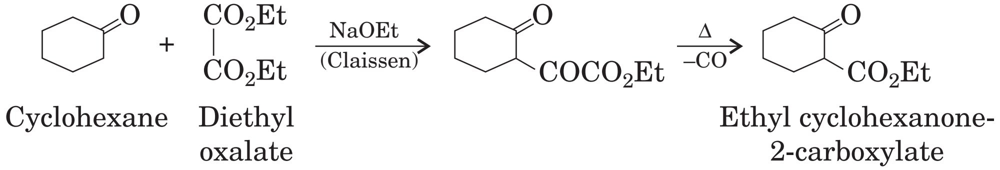


The starting materials are prepared as follows:

(i)

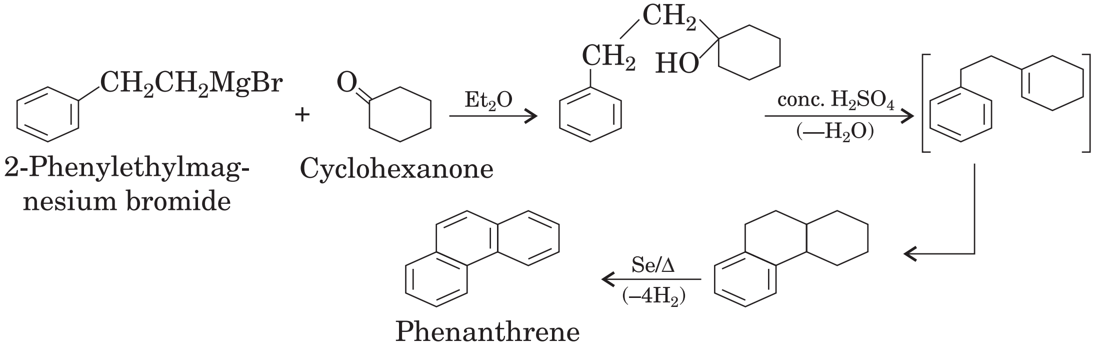


(ii)



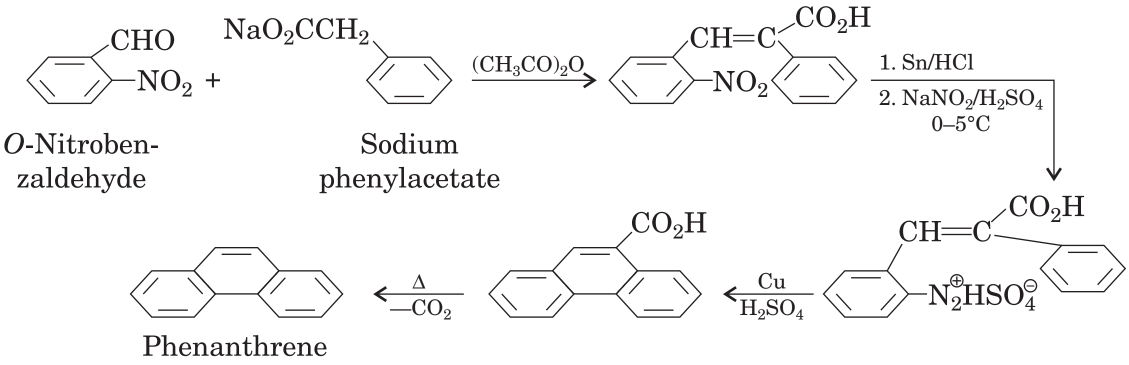
5.3.3.3 *Bogart–Cook Synthesis*

This method involves treatment of 2-phenylethylmagnesium bromide with cyclohexanone and cyclization of the resulting tertiary alcohol with concentrated sulphuric acid or phosphorus pentoxide followed by aromatization by heating with selenium.



5.3.3.4 *Pschoor Synthesis*

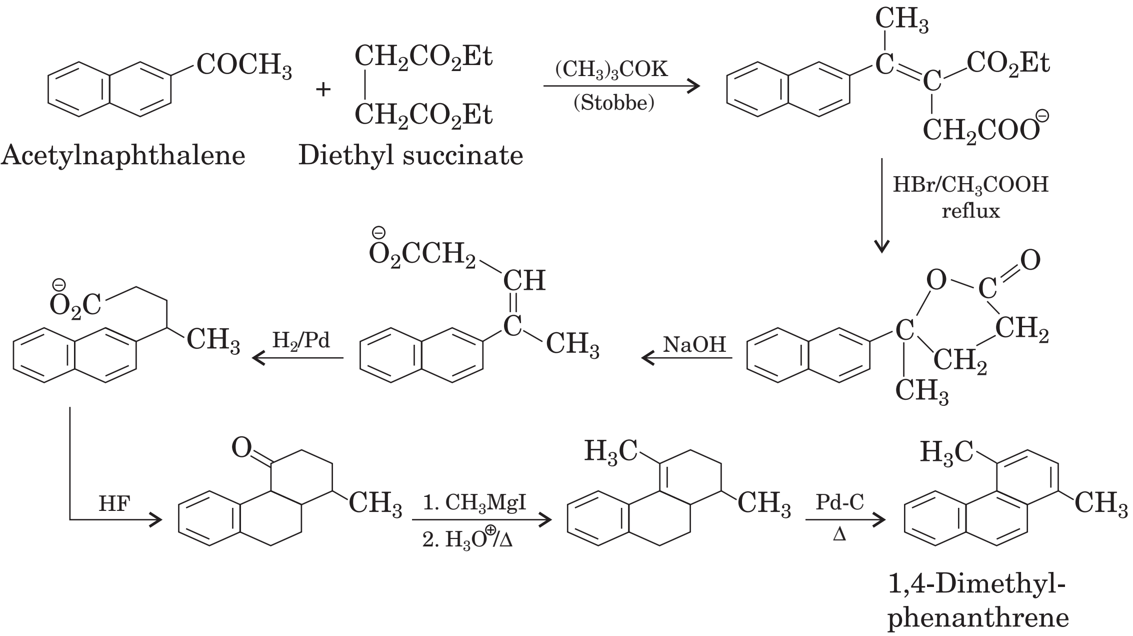
This method provides a means of preparing phenanthrene and substituted phenanthrenes with substituents in known positions. The synthesis of phenanthrene may be outlined as follows:



o-Nitrobenzaldehyde is subjected to the Perkin reaction with sodium phenylacetate in the pressence of acetic anhydride to produce *α*-phenyl-*o*-nitrocinnamic acid. This nitro acid on reduction produces the corresponding amino acid which is then diazotized. The resulting diazonium salt is treated with Cu and H_2SO_4. Phenanthrene-9-carboxylic acid is produced and this on strong heating, forms phenanthrene.

5.3.3.5 Johnson Method

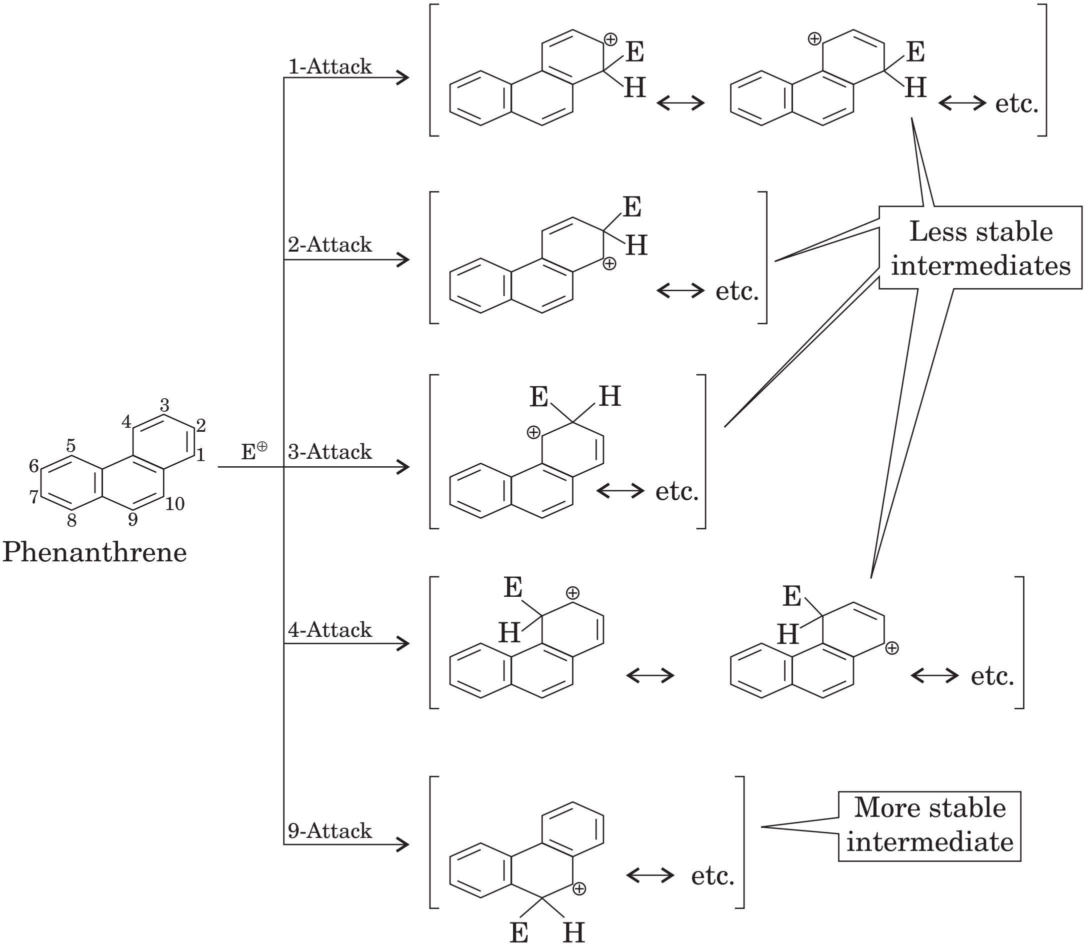
This method has been used to prepare phenanthrene derivatives by using the Stobbe condensation reaction. For example, 1,4-dimethylphenanthrene can be prepared from 2-acetylnaphthalene as follows:

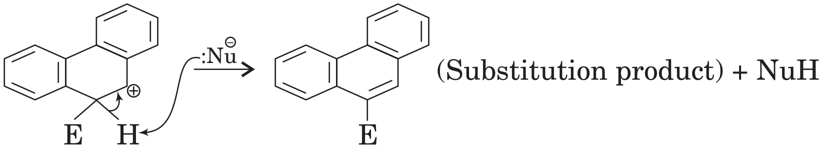


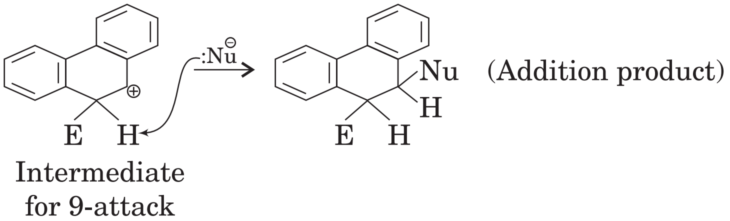
5.3.4 Reactions of Phenanthrene

5.3.4.1 Electrophilic substitutions

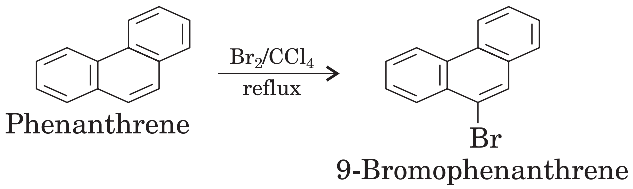
Phenanthrene undergoes electrophilic substitution reaction at 9-position and addition reaction at 9,10-positions. The electrophilic attack at 1-, 2-, 3- or 4-positions leads to an intermediate carbocation (*σ*-complex) in which a naphthalene moiety is retained, whereas the electrophilic attack at 9-position gives an intermediate carbocation in which two benzene rings are retained. Since the resonance energy of two benzene rings (2 × 36 = 72 kcal/mol), the intermediate for 9-attack is most stable among the five, electrophilic substitution occurs at 9-position and addition occurs at 9,10-positions.


1-Attack
2-Attack
3-Attack
4-Attack
9-Attack
E⊕
Phenanthrene
E
H
etc.
Less stable intermediates
More stable intermediate


:Nu⊖
E
H
(Substitution product) + NuH


:Nu⊖
Nu
E
H
(Addition product)
Intermediate for 9-attack

(i) Bromination When bromine is added to a refluxing solution of phenanthrene in carbon tetrachloride, 9-bromophenanthrene is obtained.



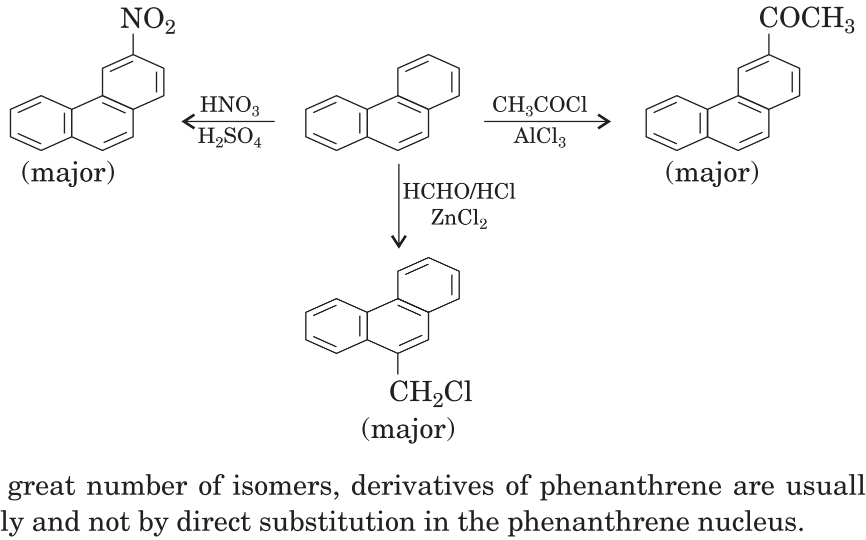
This is, in fact, the starting material for the synthesis of 9-substituted phenanthrenes. For example, when heated with cuprous cyanide at 260°C, 9-bromophenanthrene forms the corresponding cyano-compound; this may be hydrolysed to phenanthrene-9-carboxylic acid.

(ii) Nitration When nitrated, phenanthrene gives 3-nitro-phenanthrene predominantly.

(iii) Sulphonation Sulphonation of phenanthrene gives a mixture of 1-, 2-, 3- and 9-phenanthrenesulphonic acids, and the ratio of these isomers depends on the temperature.

(iv) Friedel–Crafts reaction Phenanthrene undergoes the Friedel–Crafts reaction mainly in the 3-position.

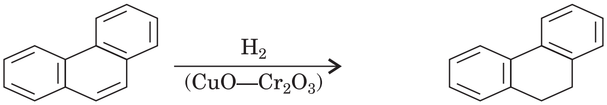
(v) Chloromethylation Phenanthrene undergoes chloromethylation mainly in the 9-position.



Because of great number of isomers, derivatives of phenanthrene are usually prepared synthetically and not by direct substitution in the phenanthrene nucleus.

5.3.4.2 Reduction

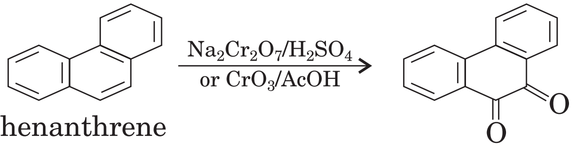
Phenanthrene is readily reduced in the presence of copper oxide-chronic oxide catalyst to give 9,10-dihydrophenanthrene.



Phenanthrene 9,10-Dihydrophenanthrene

5.3.4.3 Oxidation

When phenanthrene is oxidized with sodium dichromate and sulphuric acid or CrO_3 is glacial acetic acid, phenanthraquinone or 9,10-dihydrophenanthrene-9,10-dione is obtained.



Phenanthrene

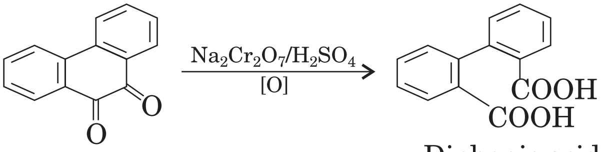
Phenanthraquinone

5.3.5 Phenanthraquinone

Phenanthraquinone may be prepared by oxidation of phenanthrene by the method given above. It is an orange solid having melting point 208°C. It is odourless and not steam-volatile.

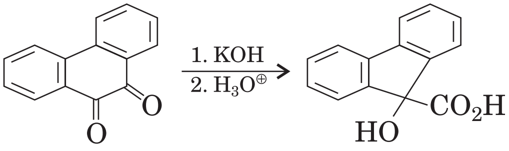
It reacts with one or two molecules of hydroxylamine to form phenanthraquinone monoxime and dioxime, respectively. It is reduced by H_2SO_3 to phenanthrene-9,10-diol (phenanthraquinol). When it is distilled with zinc dust, phenanthrene is obtained.

When nitrated, phenanthraquinone produces a mixture of 2- and 4-nitrophenanthraquinones. Oxidation with $Na_2Cr_2O_7$ and H_2SO_4 converts phenanthraquinone into diphenic acid.

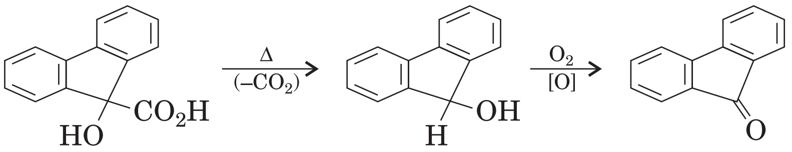


Phenanthraquinone Diphenic acid

When warmed with alkali, phenanthraquinone undergoes the benzilic acid rearrangement to yield 9-hydroxyfluorene-9-carboxylic acid.

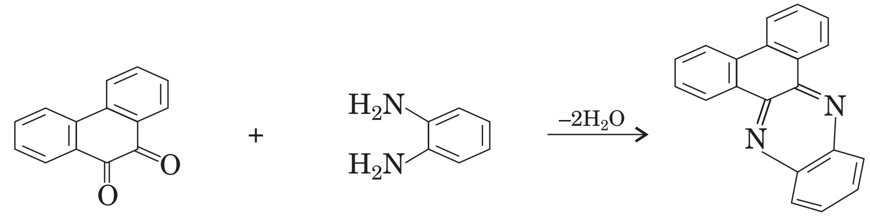


When this acid is heated in air, it undergoes decarboxylation to give fluorenol which readily undergoes oxidation to give fluorenone.



Fluorenol Fluorenone

Phenanthraquinone readily combines with *o*-phenylenediamines to form phenazines which are useful for characterizing *o*-phenylenediamines and this is because they are insoluble in many organic solvents. For example:

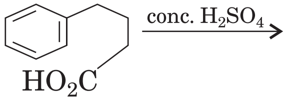


Phenanthraquinone *o*-Phenylenediamine (insoluble)

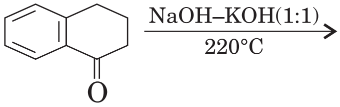
SOLVED PROBLEMS

1. **Predict the product and suggest a mechanism for each of the following reactions:**

(a)

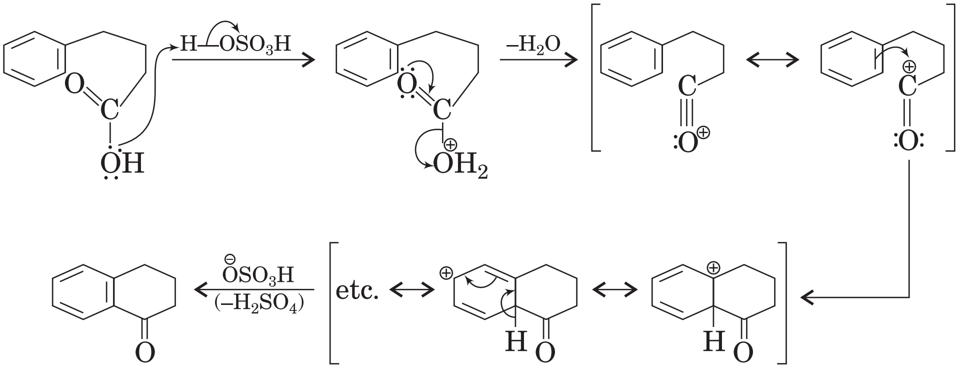


(b)



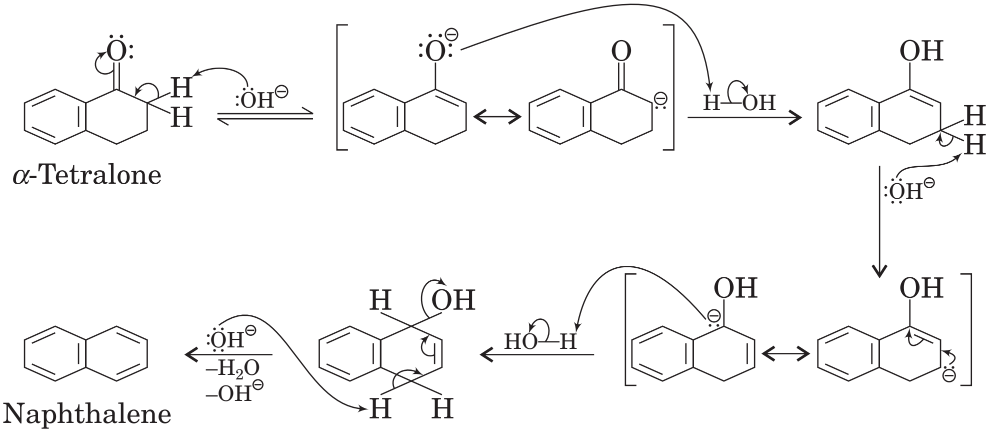
Solution

(a) In the presence of strong acid (powerful ionizing medium), protonation occurs on the less favoured hydroxyl oxygen instead of carbonyl oxygen to produce, after water loss, an acylium ion. Intramolecular acylation yields α-tetralone.



α-Tetralone

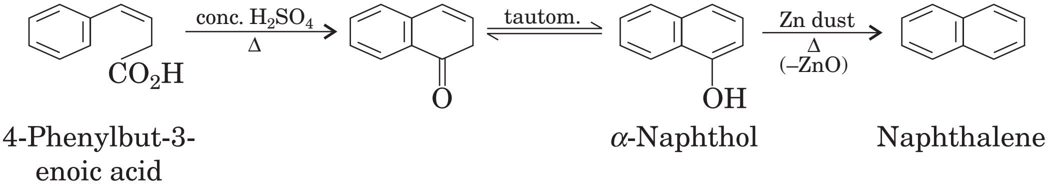
(b) When α-tetralone is heated with a 1:1 mixture of NaOH-KOH at 220°C, naphthalene is obtained.
The mechanism of the reaction involves tutomerization followed by base-catalyzed rearrangement and dehydration



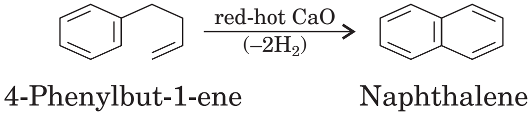
2. **What happens when: (a) 4-phenylbut-3-enoic acid is heated with concentrated sulphuric acid and the resulting compound is heated with Zn dust, (b) 4-phenylbut-1-ene is passed over red-hot CaO (catalyst).**

Solution

(a) When 4-phenylbut-3-enoic acid is heated with conc. H_2SO_4, it undergoes cyclization to form α-naphthol which on heating with Zn dust yields naphthalene.

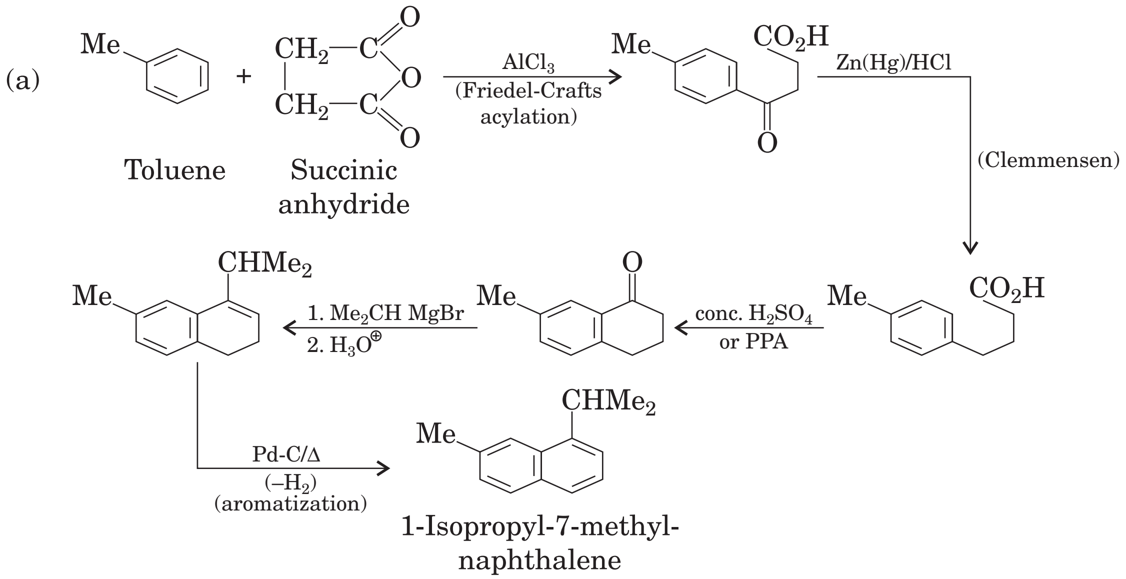


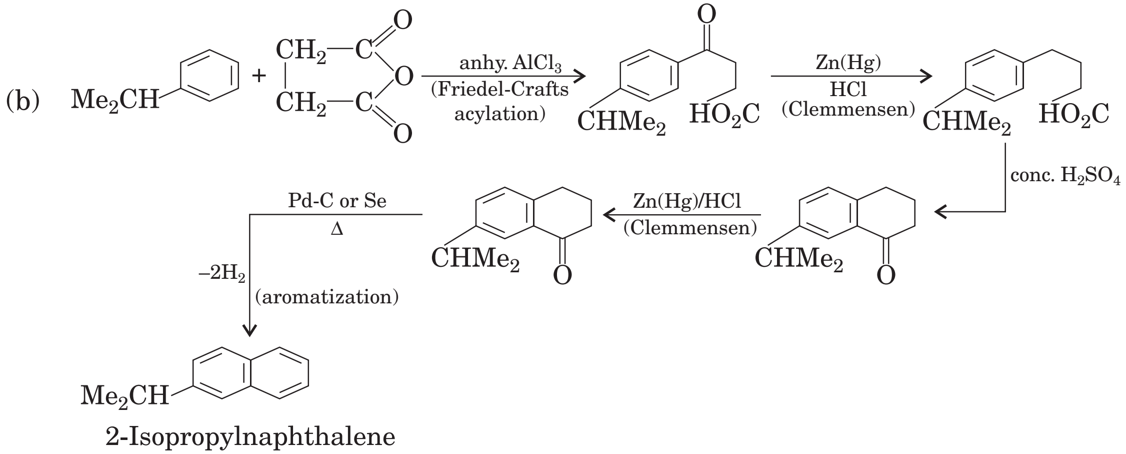
(b) When 4-phenylbut-1-ene is passed over red-hot CaO, naphthalene is obtained as a result of elimination of two H_2 molecules.



3. How would you prepare the following compounds by Haworth Synthesis? (a) 1-Isopropyl-7-methylnaphthalene (b) 2-isopropylnaphthalene

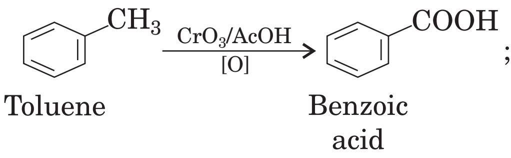
Solution



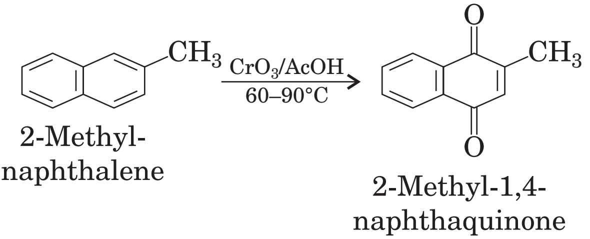


4. Predict the products expected to be formed when toluene and 2-methylnaphthalene are oxidized by CrO_3/AcOH and explain.

Solution The methyl group of toluene ($PhCH_3$) is more susceptible to oxidation than the aromatic ring and so, the oxidation product is benzoic acid (PhCOOH). On the other hand, in 2-methylnaphthalene, the reactive 1-positions are more easily oxidized than methyl and so, under these conditions of oxidation, the predominant product is 2-methyl-1,4-naphthaquinone.



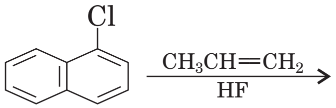
Toluene ; Benzoic acid



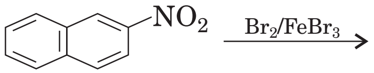
2-Methylnaphthalene ; 2-Methyl-1,4-naphthaquinone

5. Give the product expected to be formed in each of the following reactions:

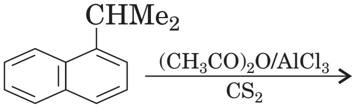
(a)



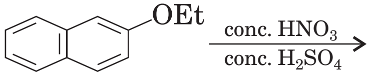
(b)



(c)

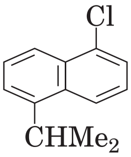


(d)



Solution Based on the concept of alternant polarity the expected products are as follows:

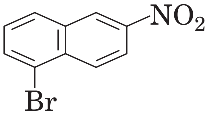
(a)



(1-Chloro-5-isopropylnaphthalene)

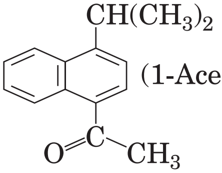
Due to *peri*-interaction at C-8, substitution occurs preferably at C-5.

(b)



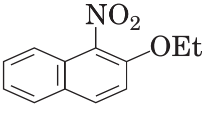
(1-Bromo-6-nitronaphthalene)

(c)



(1-Acetyl-4-isopropylnaphthalene)

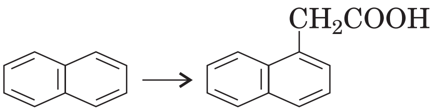
(d)



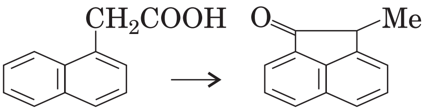
(2-Ethoxy-1-nitronaphthalene)

6. How would you carry out the following transformations?

(a)



(b)



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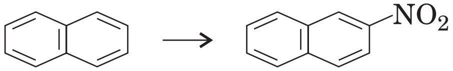
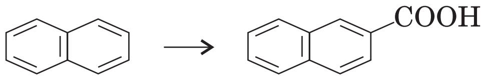
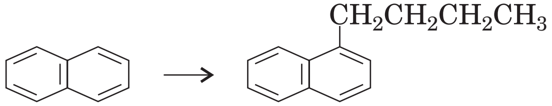


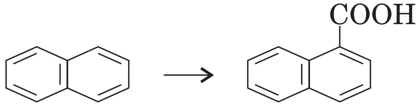
(d)



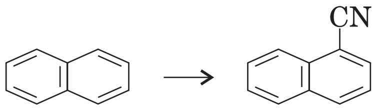
(e)



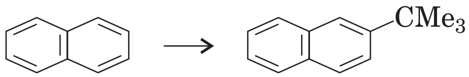
(f)



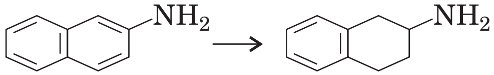
(g)



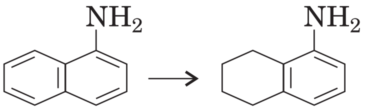
(h)



(i)



(j)



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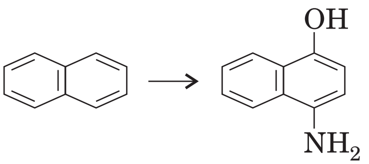

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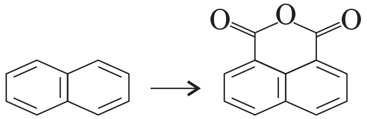

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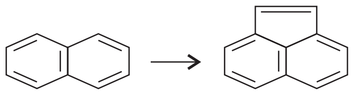
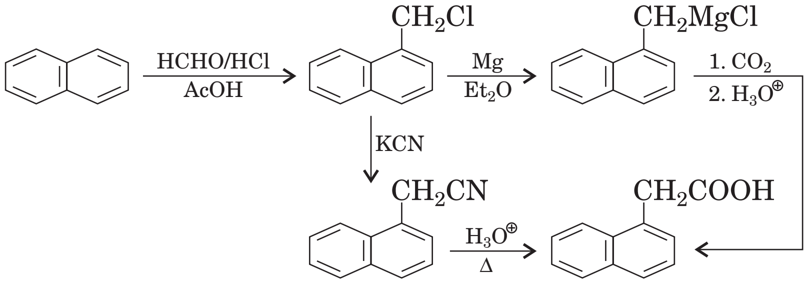
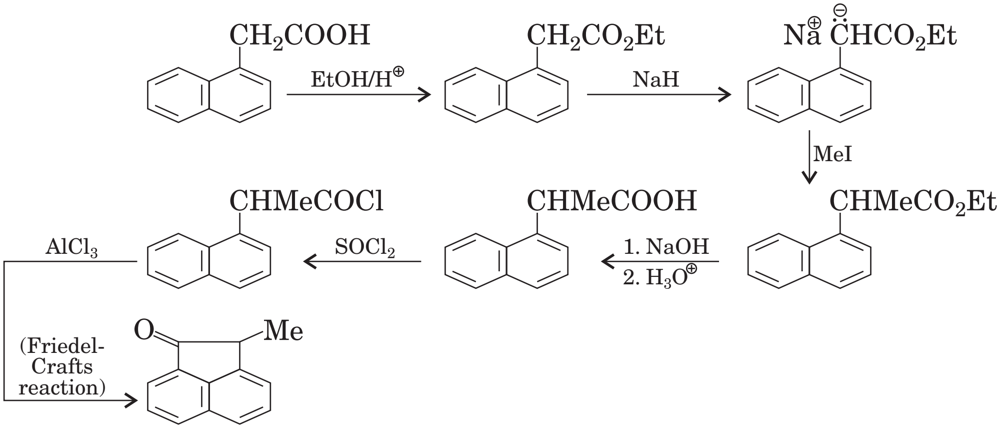


Solution

(a)



(b)



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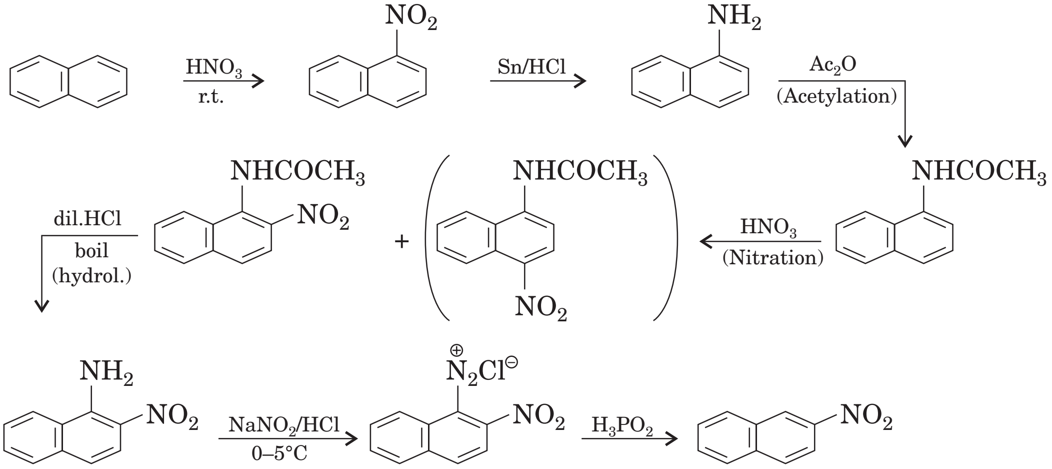
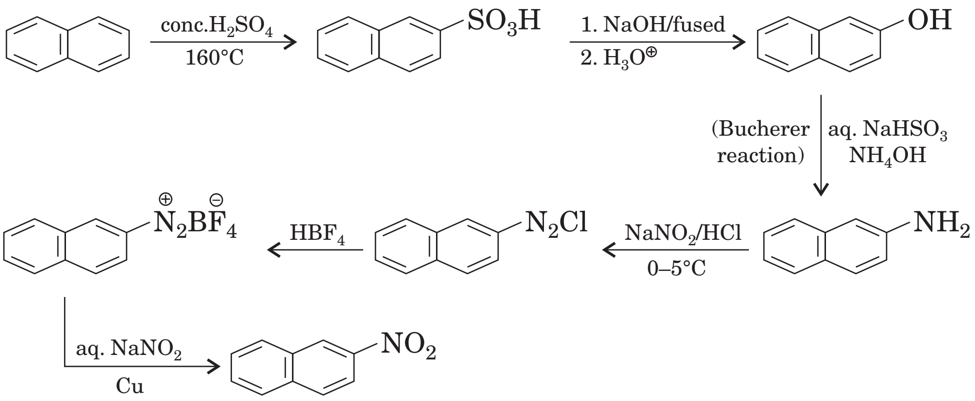


Alternate process:



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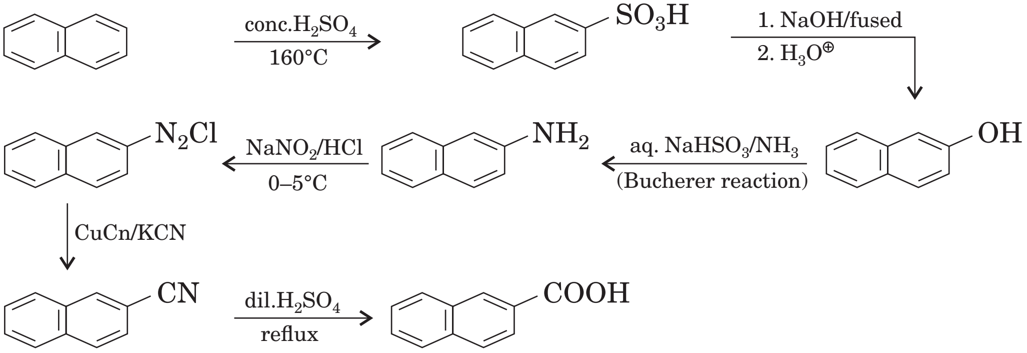

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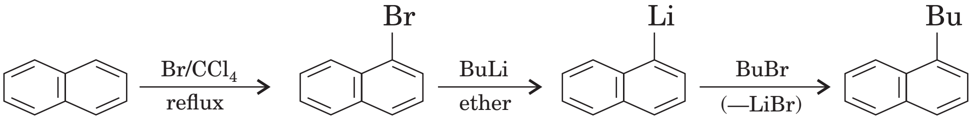

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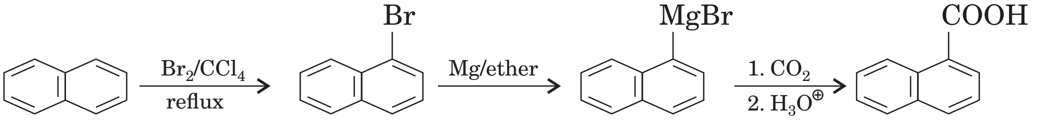

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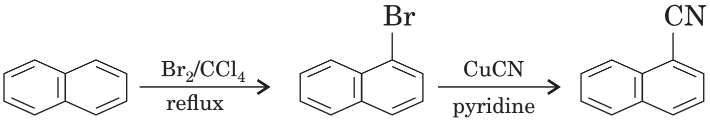

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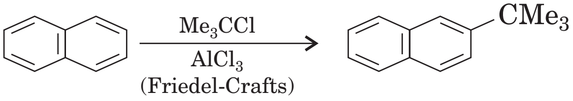
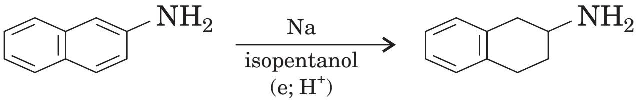


The Friedel-Crafts reaction is reversible in nature and so the bulky *t*-butyl group enters at 2-position to avoid steric interaction (*peri*-interaction) with C-8 hydrogen.

(i)


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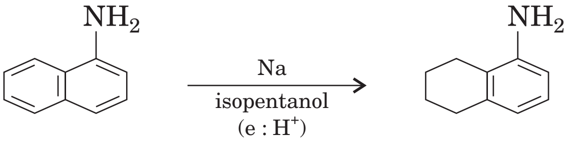

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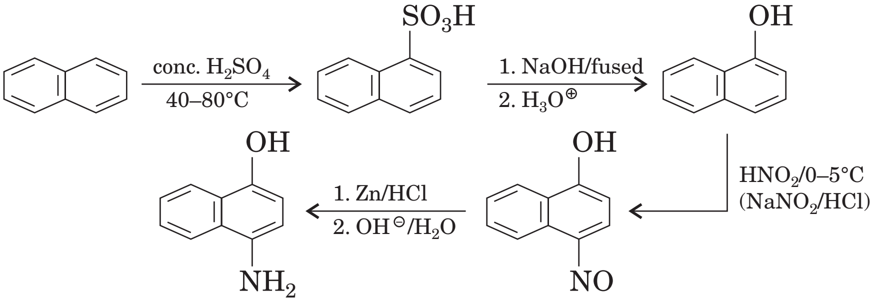

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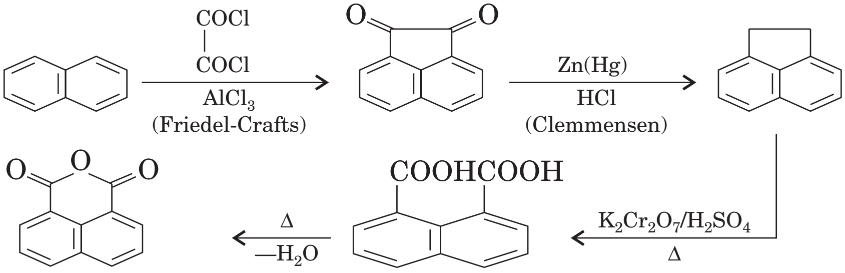
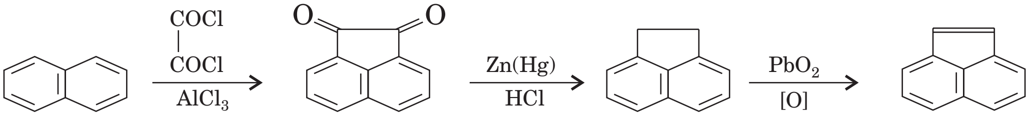


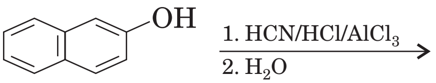
1,8-Naphthalic anhydride

(m)


Acenaphthene

7. Predict the product and suggest a mechanism for each of the following reactions:

(a)



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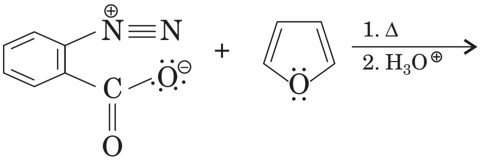
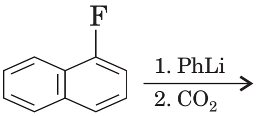
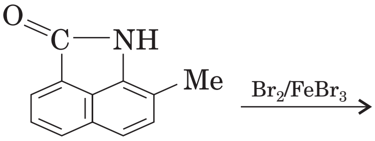


(c)



(d)



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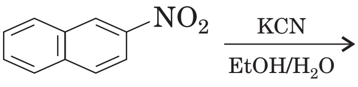

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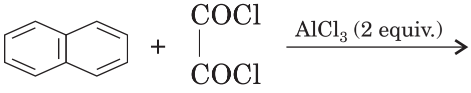
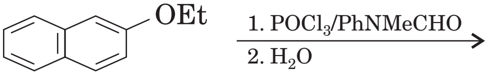


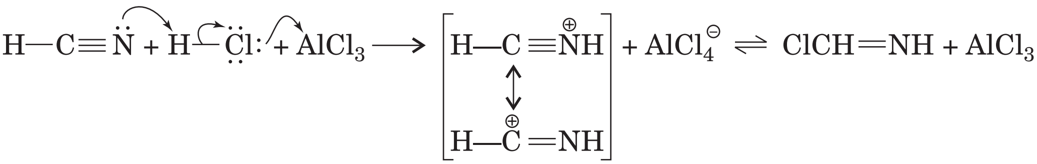
(g)



Solution

(a) *β*-Naphthol undergoes the Gattermann reaction to yield 2-hydroxy-1-naphthaldehyde when treated with a mixture of HCN, HCl and $AlCl_3$ followed by water. The mechanism of the reaction which is, in fact, an electrophilic aromatic substitution, is as follows:

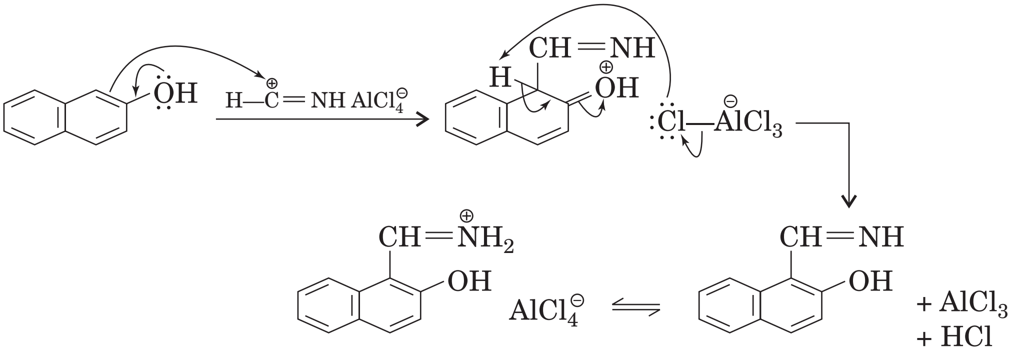
The electrophile involved in this reaction is the formaldiminium ion $(\mathrm{H{-}\overset{\oplus}{C}{=}NH})$ which is formed as follows:



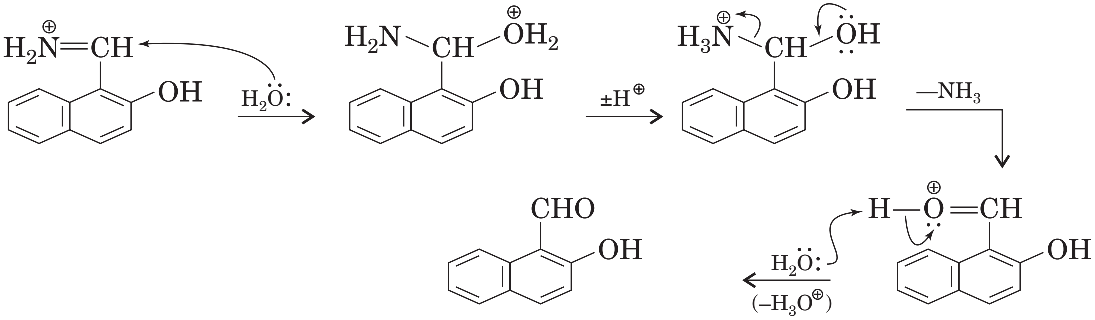
$$\mathrm{H{-}C{\equiv}\ddot{N} + H{-}\ddot{C}l\!: + AlCl_3 \longrightarrow \left[\begin{array}{c}\mathrm{H{-}C{\equiv}\overset{\oplus}{N}H}\\ \updownarrow \\ \mathrm{H{-}\overset{\oplus}{C}{=}NH}\end{array}\right] + AlCl_4^{\ominus} \rightleftharpoons ClCH{=}NH + AlCl_3}$$

Formaldiminium ion

The substitution reaction then takes place through the formation of a *σ*-complex.



When the complex so produced is decomposed with water 2-hydroxy-1-naphthaldehyde is obtained.



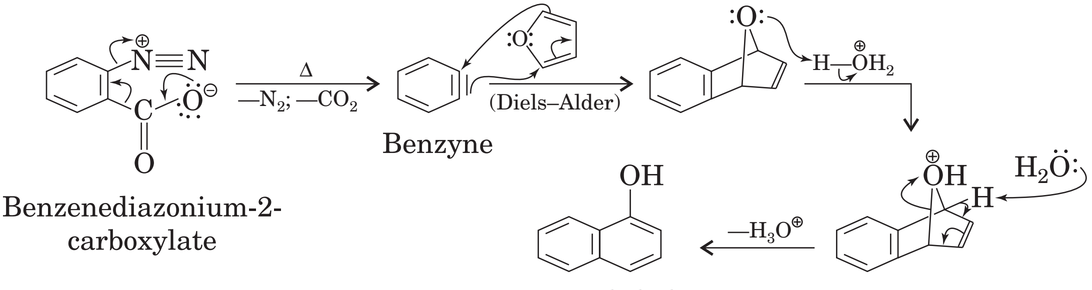
2-Hydroxy-1-naphthaldehyde

[Instead of $AlCl_3$, $Zn(CN)_2$ may be used and in that case the electrophile, formaldiminium ion, is generated as follows:

$$Zn(CN)_2 + 2HCl \rightleftharpoons ZnCl_2 + 2HCN\ ;\ ZnCl_2 + 2HCl \rightleftharpoons 2H^{\oplus} + ZnCl_4^{2\ominus}$$

$$2\,H{-}C{\equiv}N + 2H^{\oplus}ZnCl_4^{2\ominus} \rightleftharpoons 2[H{-}C{\equiv}\overset{\oplus}{N}H \longleftrightarrow H{-}\overset{\oplus}{N}{=}NH] + ZnCl_4^{2\ominus}]$$

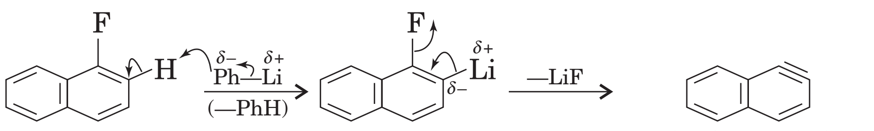
(b) Benzyne, generated by heating benzene diazonium-2-carboxylate adds to furan (a Diels–Alder reaction) to form a cyclic ether which on acid-catalyzed decomposition yields α-naphthol.



Benzenediazonium-2-carboxylate

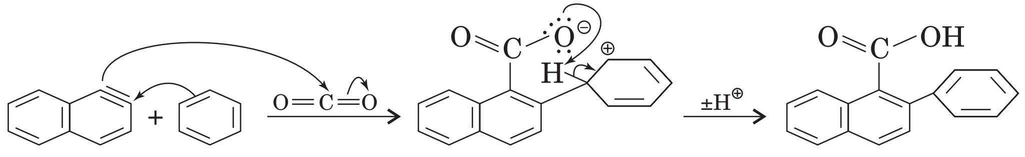
α-Naphthol

(c) 1-Fluoronaphthalene reacts with phenyllithium to form 1,2-dehydronaphthalene (an aryne) which subsequently reacts with CO_2 and benzene to yield 2-phenyl-1-naphthoic acid (I) and 1-phenyl-2-naphthoic acid (II).

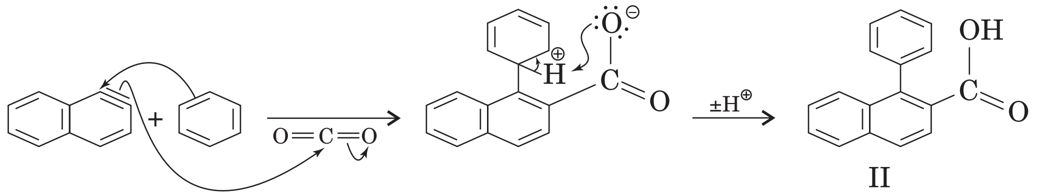


1,2-Dehydronaphthalene

Then

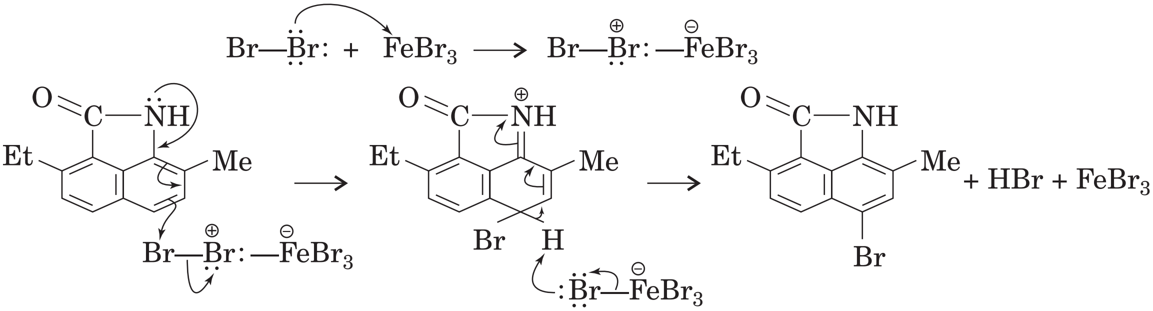


I

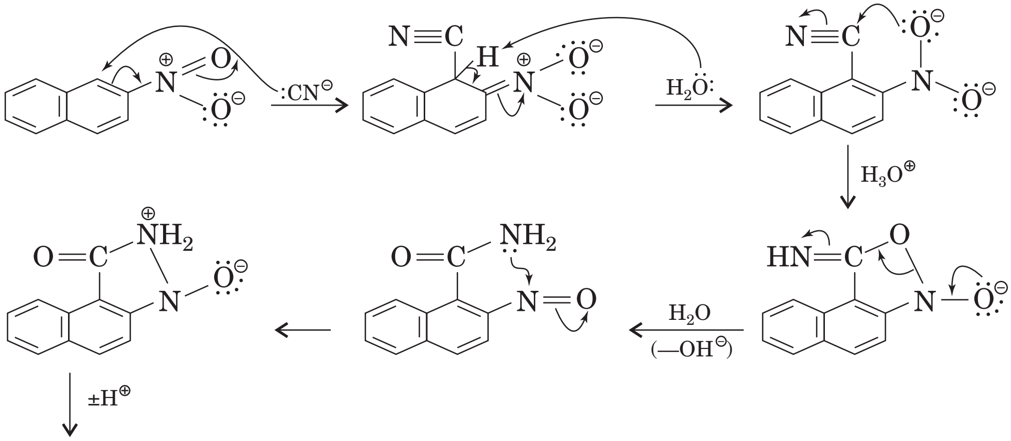


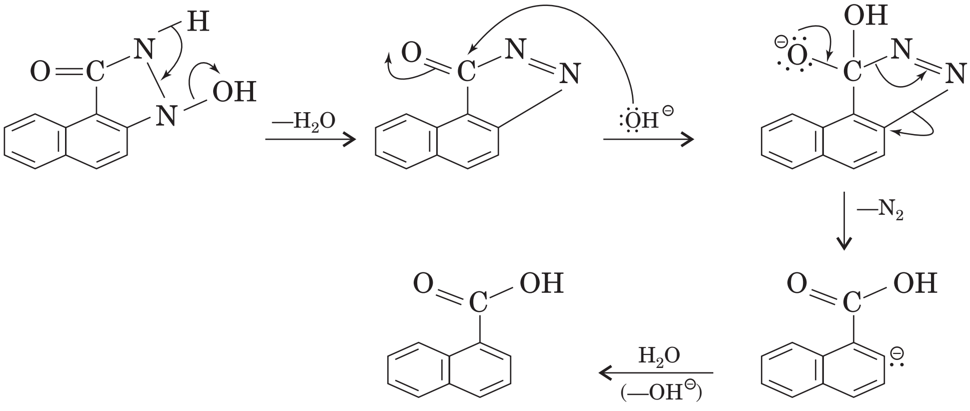
II

(d) The ring attached to nitrogen is more activated, whereas the ring attached to carbonyl is deactivated towards electrophilic aromation substitution. Therefore, the former ring undergoes bromination in the presence of $Br_2/FeBr_3$ to give the corresponding *p*-bromoderivative.

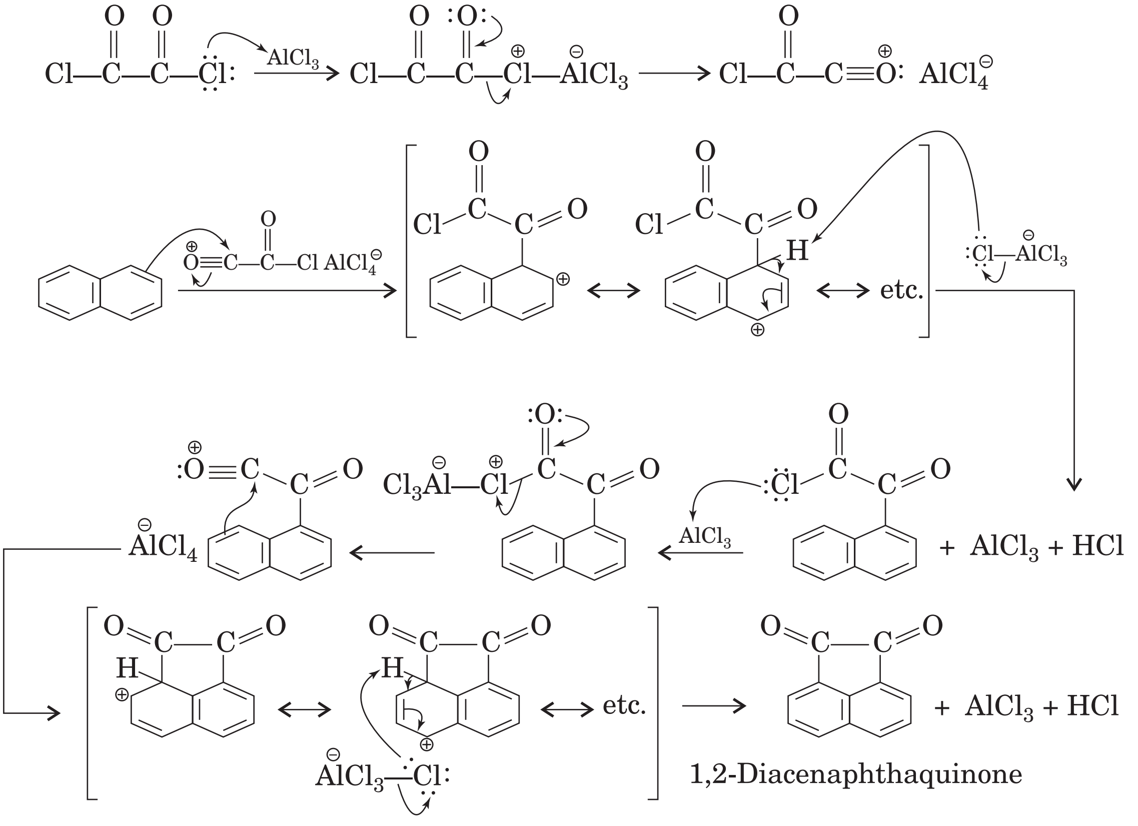


(e) 2-Nitronaphthalene undergoes *von Richter reaction* when treated with aqueous ethanolic potassium cyanide to yield 1-naphthalene carboxylic acid.



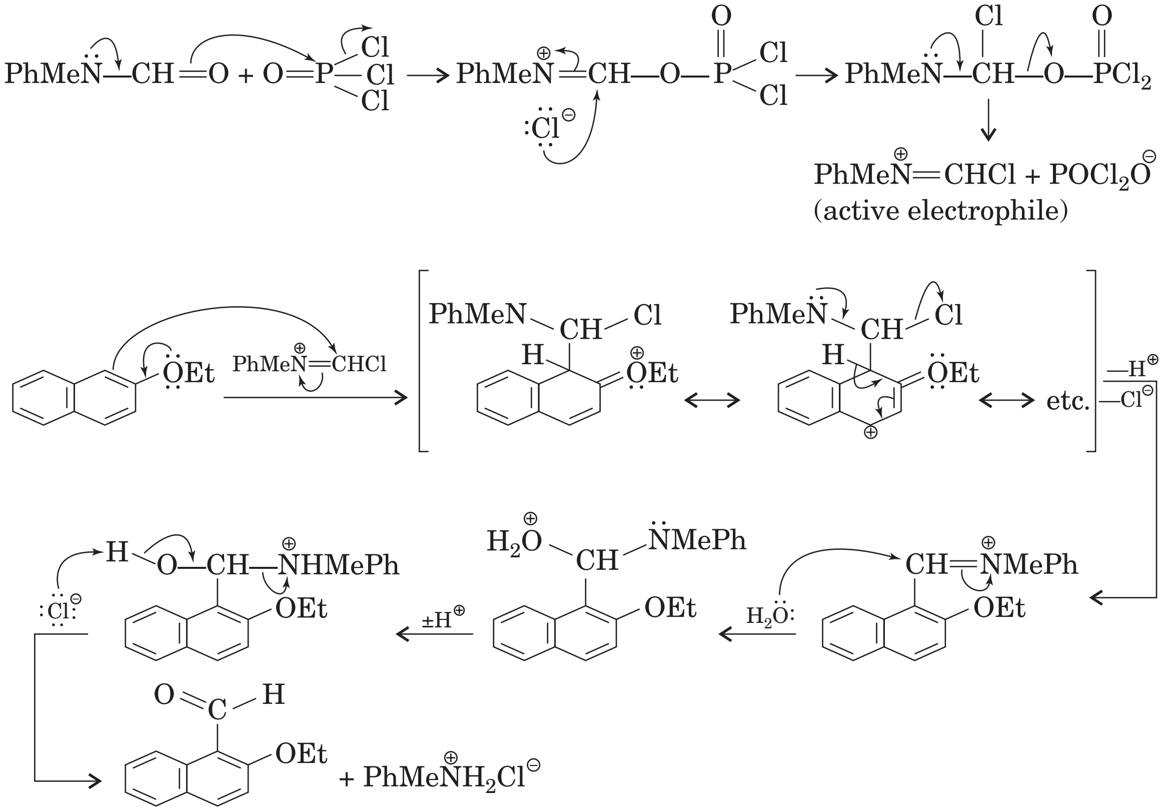


(f) Naphthalene undergoes Friedel-Crafts acylation at C-1 and C-8 by oxalyl chloride in the presence of anhydrous AlCl$_3$ to form 1, 2-diacenaphthaquinone.

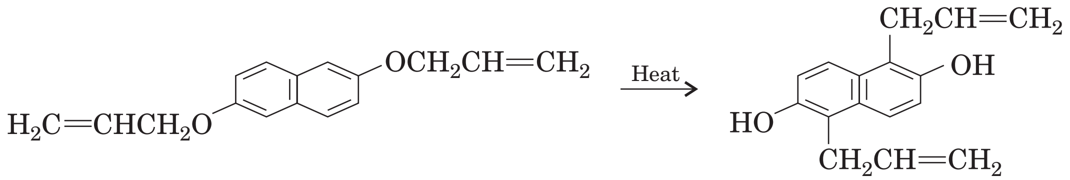


1,2-Diacenaphthaquinone

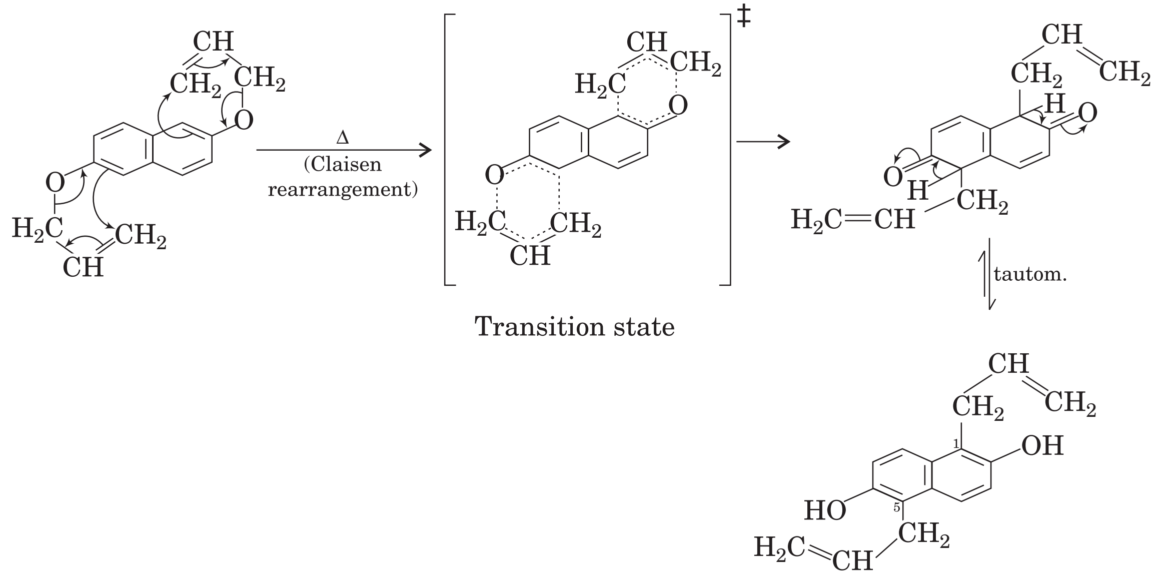
(g) 2-Ethoxynaphthalene undergoes Vilsmeier–Haak formylation at C-1 when treated with PhNMeCHO in the presence of phosphorus oxychloride ($POCl_3$) followed by treating the resultant iminium ion with water.



8. Propose a curved-arrow mechanism for the following reaction and explain why the 1,5-diallyl derivative and not 3,7-diallyl derivative is obtained:



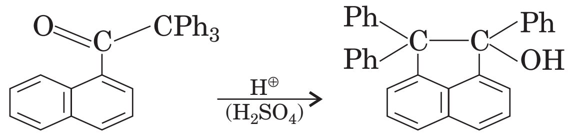
Solution This is an example of *ortho*-Claisen rearrangement. The reaction takes place through a six-membered cyclic transition state as follows:



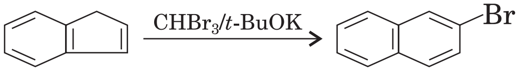
Because of fixed bond structure of naphthalene, migration occurs to give 1,5-diallyl derivative and not 3,7-diallyl derivative.

9. Give a curved-arrow mechanism for each of the following reactions:

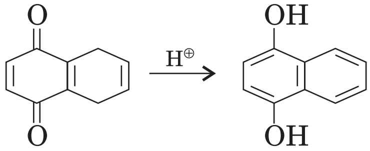
(a)



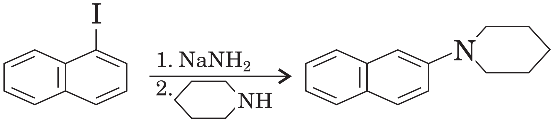
(b)



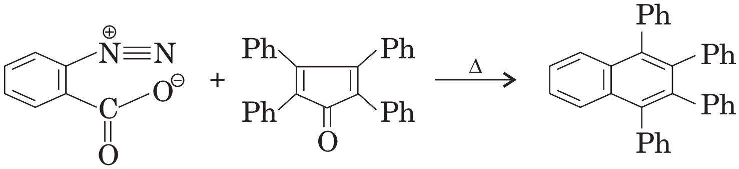
(c)



(d)

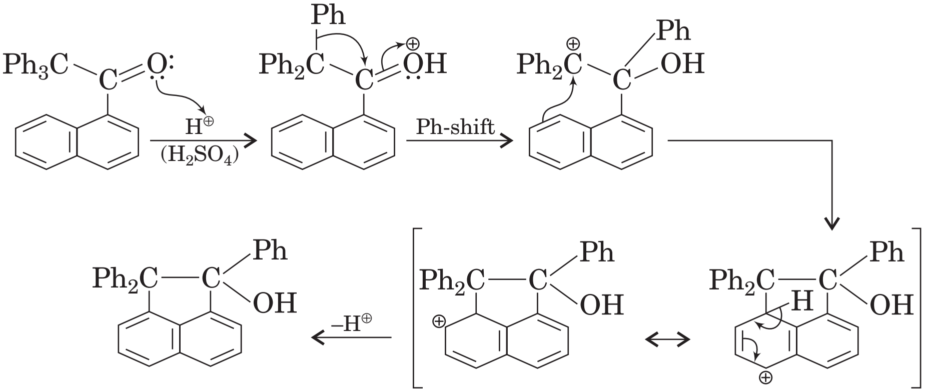


(e)

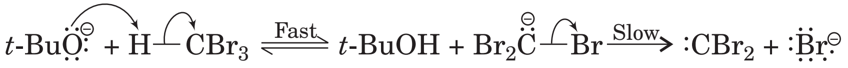


Solution

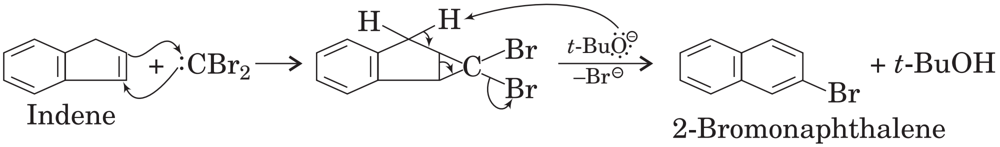
(a) This is a case of acid-catalyzed rearrangement followed by an intramolecular electrophilic aromatic substitution.



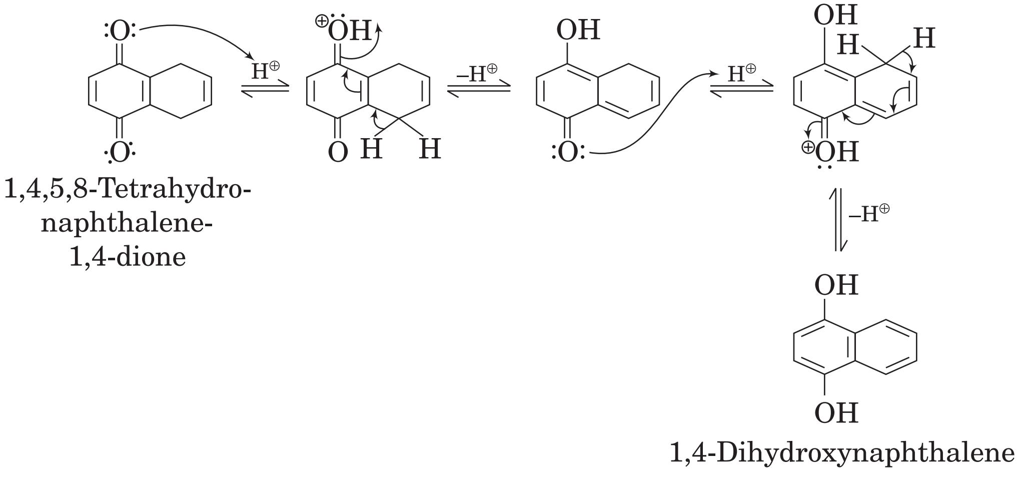
(b) Bromoform reacts with t-BuO$^{\ominus}$ to form the electrophilic species dibromocarbene which then adds to indene to form a cyclopropane derivative. This eliminates a molecule of HBr in the presence of base to yield 2-bromonaphthalene.



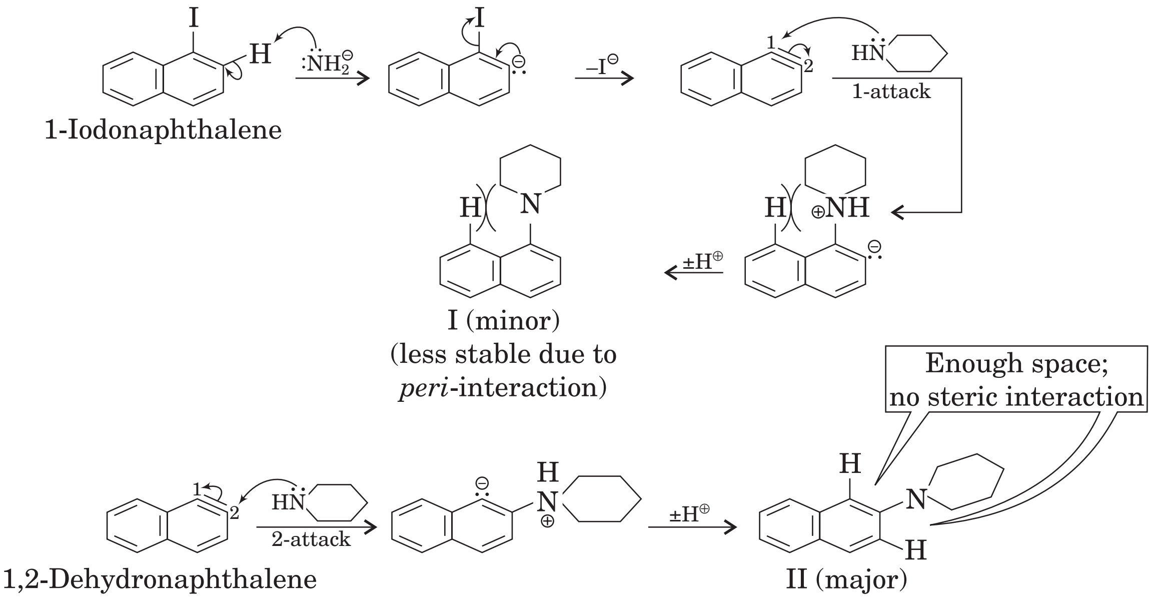
$$t\text{-Bu}\ddot{\underset{..}{O}}{:}^{\ominus} + H-CBr_3 \overset{\text{Fast}}{\rightleftharpoons} t\text{-BuOH} + Br_2\overset{\ominus}{\ddot{C}}-Br \xrightarrow{\text{Slow}} {:}CBr_2 + {:}\ddot{\underset{..}{Br}}{:}^{\ominus}$$



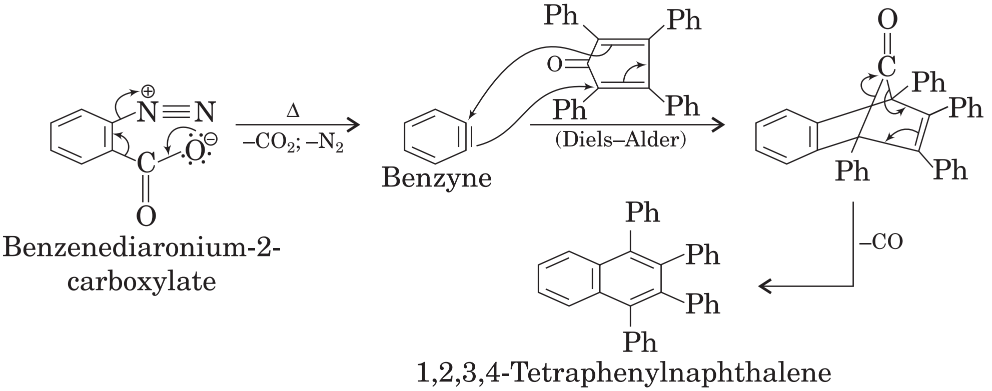
(c) It is a case of double enolization which takes place in the presence of acid to form the aromatic system 1,4-dihydroxynaphthalene.



(d) 1-Iodonaphthalene reacts with sodamide to form 1,2-dehydronaphthalene (an aryne). This aryne then adds to piperidine to give the normal (I) and *cine*-substitution product (II). Because of steric interaction with C-8 H-atom (*peri*-interaction), the product II is the major product.

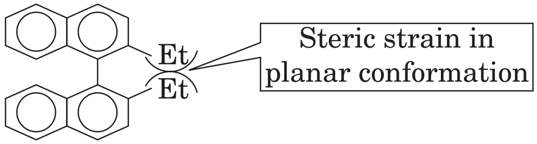


(e) Benzyne, obtained on thermal decomposition of benzenediazonium-2-carboxylate adds to tetraphenylcyclopentadienone (a Diels–Alder reaction) to give an adduct which under the reaction conditions eliminates a molecule of carbon monoxide to yield 1,2,3,4-tetraphenylnaphthalene.

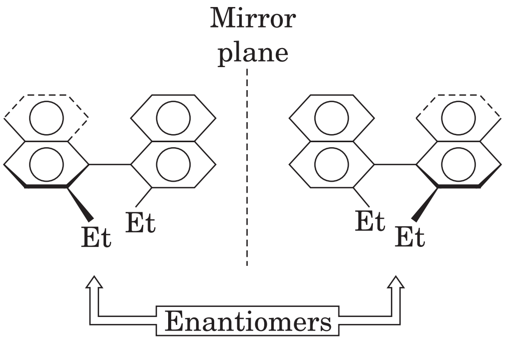


10. Give the product expected to be obtained when 1-iodo-2-ethylnaphthalene is subjected to the Ullmann reaction. Is the coupling product chiral? Give reasons.

Solution The structure of the product obtained in this reaction may be given as follows:

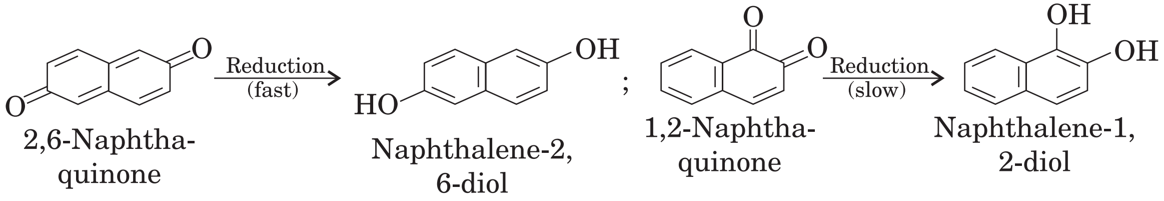


The compound is axially chiral. Because of steric interaction between the two bulky *ortho*-substituents, the two rings cannot be coplanar and in fact, they remain orthogonal to each other. Because of axial chirality then arises, the compound is able to exist in two enantiomeric forms.



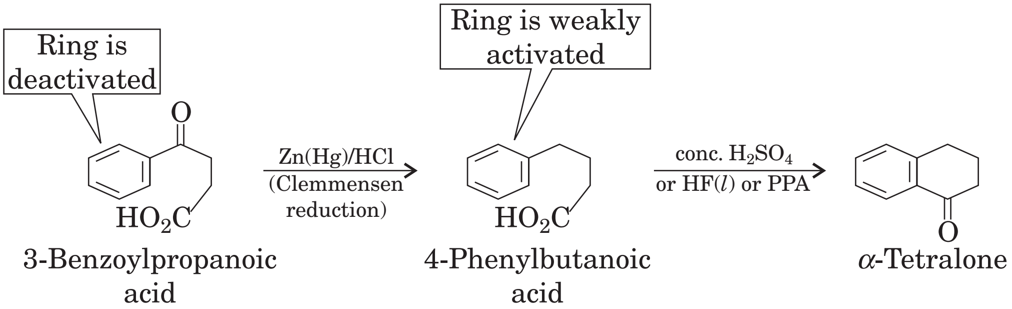
11. **Explain why 2,6-naphthaquinone undergoes reduction to give the corresponding diol at a rate faster than 1,2-naphthaquinone.**

Solution 1,2-Naphthaquinone contains only one benzene ring. On reduction, it becomes converted into naphthalene-1,2-diol and as a result, the thermodynamic stability of the molecule increases due to gain of aromaticity of one ring. On the other hand, 2,6-naphthaquinone has no benzene ring. Since reduction causes aromatization of both the rings, it gains more stabilization. For this reason, 2,6-naphthaquinone undergoes reduction more readily than 1,2-naphthaquinone.

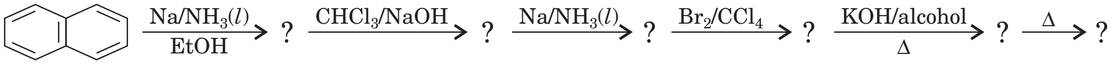


12. **In Haworth synthesis of naphthalene, the Clemmensen reduction is carried out before ring closure—Why?**

The carbonyl group in the ketoacid obtained on succinoylation of benzene deactivates the ring by its –R effect. Because of this, effective ring closure of the ketoacid in the presence of concentrated H_2SO_4 or HF (l) or PPA (an electrophilic aromatic substitution) does not take place. For an effective ring closure, the $>C{=}O$ group is reduced by Clemmensen method to a moderately activating alkyl group.

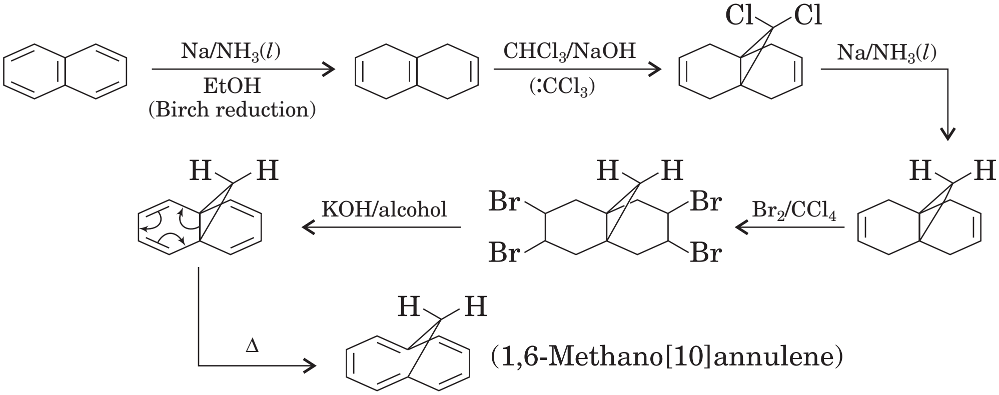


13. Predict the product obtained in each step of the following reaction sequence:



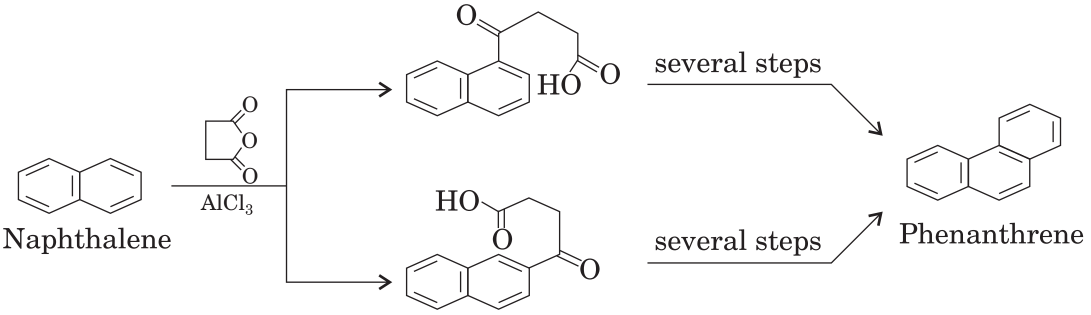
Give the mechanism of the final step?

Solution

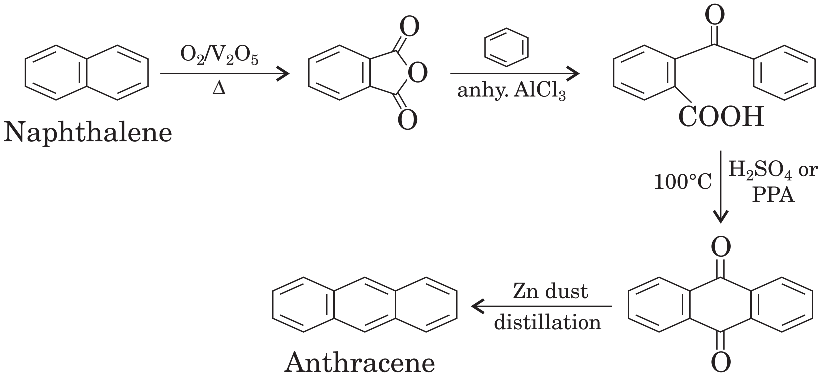


14. Explain why anthracene cannot be prepared by succinoylation of naphthalene. How can anthracene be prepared from naphthalene?

Solution Succinoylation (a Friedel–Crafts acylation with succinic anhydride in the presence of $AlCl_3$) is an electrophilic aromatic substitution. Electrophilic substitution in naphthalene occurs at C-1 or C-2 position. Formation of anthracene requires succinoylation at C-2 followed by ring closure at C-3. However, due to fixed bond character, ring closure after succinoylation occurs not at C-3 but at C-1. Therefore, the new benzene ring which is generated is always angularly fused to the naphthalene ring, i.e., phenanthrene instead of anthracene is obtained finally.

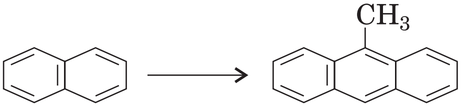


Anthracene can be prepared from naphthalene as follows:

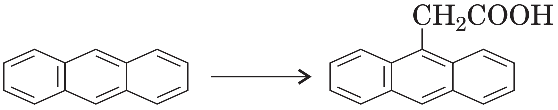


15. How would you carry out the following transformations?

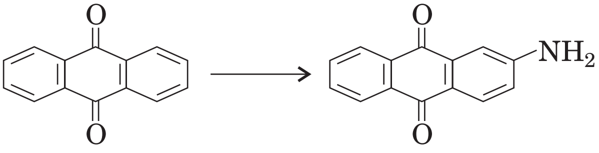
(a)



(b)

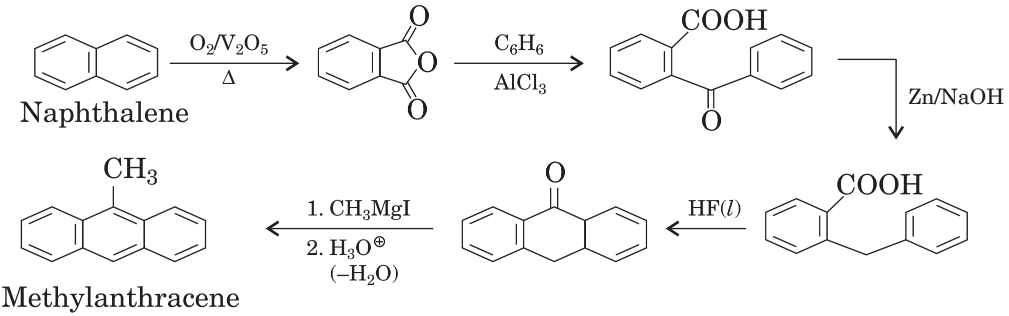


(c)

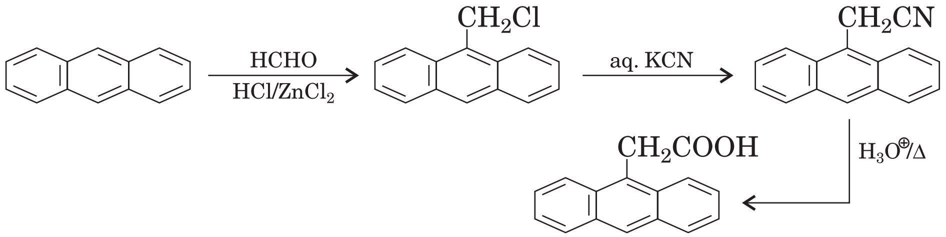


Solution

(a)



(b)



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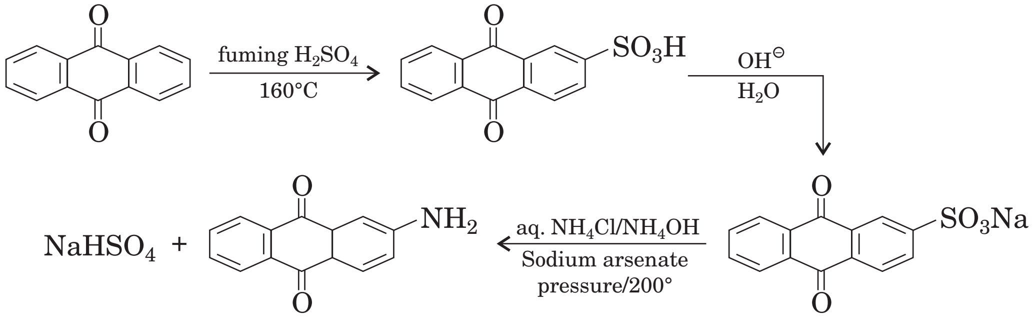
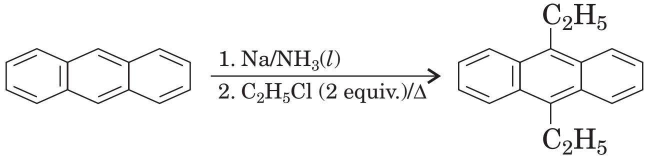


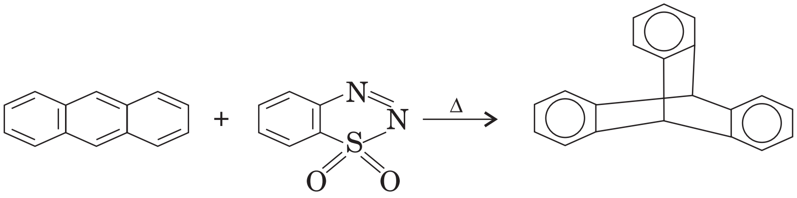
Sodium arsenate oxidizes the liberated sulphite which otherwise would attack the amine produced.

16. Give a curved-arrow mechanism for each of the following reactions:

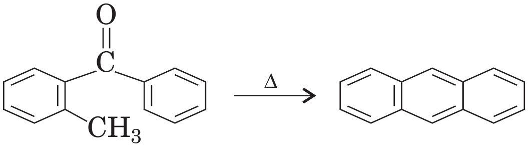
(a)



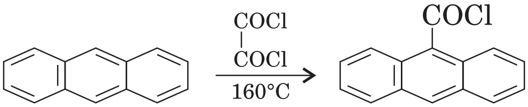
(b)



(c)



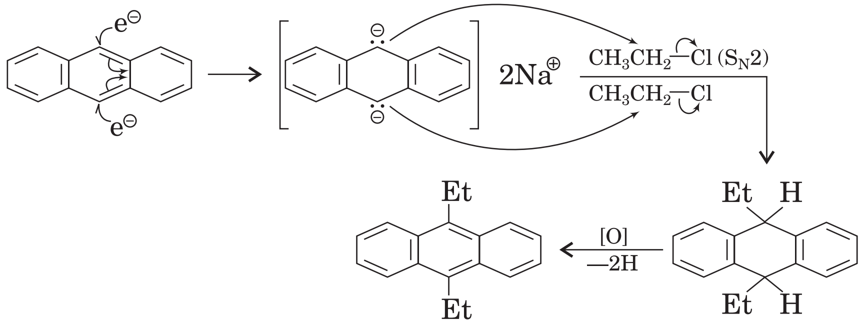
(d)



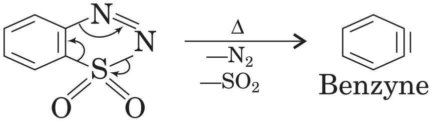
Solution

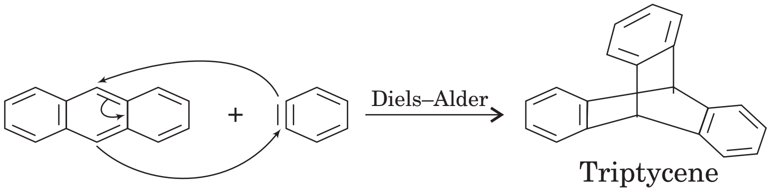
(a) Anthracene reacts with Na in liquid NH_3 to give 9,10-disodioanthracene (a deep blue compound) which when heated with ethyl chloride, produces 9,10-diethylanthracene.

$$NH_3(l) + Na \rightleftharpoons \underset{\text{(solvated electron)}}{e^{\ominus}(NH_3)_n} + Na^{\oplus}$$



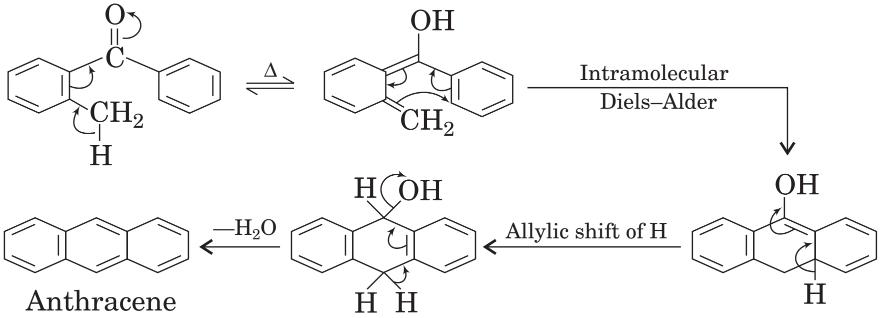
9,10-Diethylanthracene

(b) 

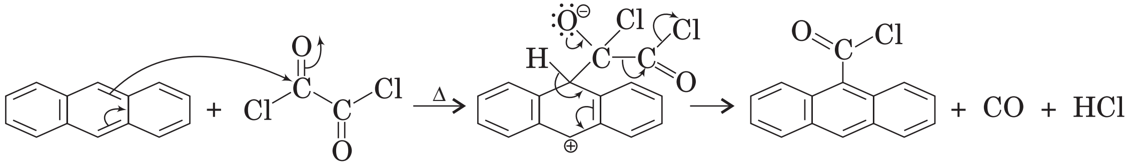
Then, 

The azo compound on thermal decomposition produces the reactive intermediate benzyne which then undergoes the Diels–Alder reaction with anthracene to yield triptycene.

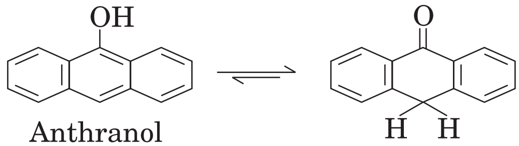
(c) The mechanism of the Elbs reaction is as follows:



(d) Under heated condition the —COCl group is introduced at C-9 of anthracene as follows:



17. How would you explain the position of the following tautomeric equilibrium?



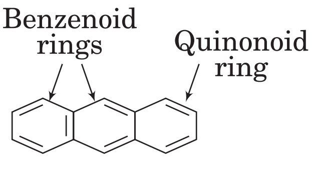
Anthranol
(enol-form)

Anthrone
(keto-form)

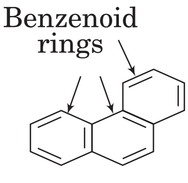
Solution The equilibrium depends on the relative resonance energies of the two tautomers. The phenolic tautomer (i.e., the enol-form) is usually stabilized by ring aromaticity. However, in this case the reverse is true. Anthrone (the keto-form) has two distinct intact aromatic rings in addition to the C=O group (bond energy is considerably higher). This causes anthrone to be more stable than anthranol, which actually suffers a loss of aromaticity per ring because it contains three fused rings. This explains why the concentration of anthone at equilibrium is higher than that of anthranol.

18. Anthracene and Phenanthrene are two isomeric polynuclear hydrocarbons with three *ortho*-fused benzene rings. Explain why phenanthrene is thermodynamically more stable than anthracene.

Solution The resonance energies of anthracene and phenanthrene are 351.5 and 387.0 kJ/mol, respectively. Hence, the latter is more stable than the former. This can be well explained by the Fries rule. In anthracene, two of the three linearly fused rings can assume benzenoid form and the other must be in the less stable quinonoid form. In phenanthrene, on the other hand, all the three rings can assume benzenoid structure. According to the Fries rule, in polynuclear hydrocarbons, that structure is most stable in which there are maximum number of benzenoid ring system. Therefore, phenanthrene is expected to be more stable than its isomer anthracene.



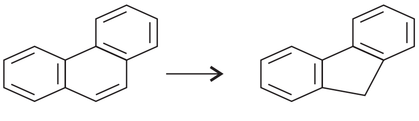
Anthracene
(the most stable structure
in which only two rings are
in benzenoid form)



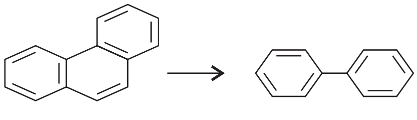
Phenanthrene
(the most stable structure
in which all the three rings
are in benzenoid form)

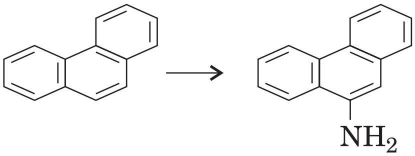
19. Suggest a method for each of the following conversions:

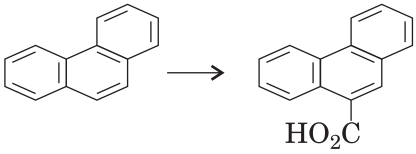
(a)

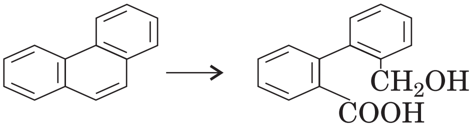


(b)

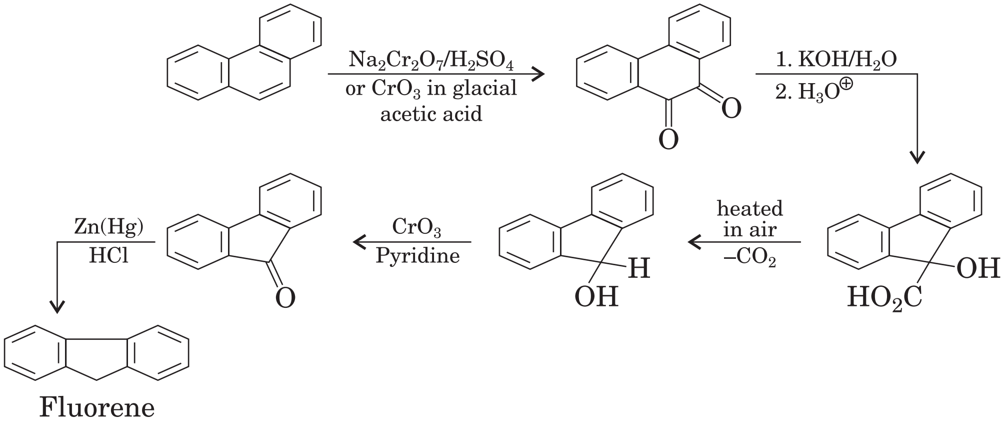


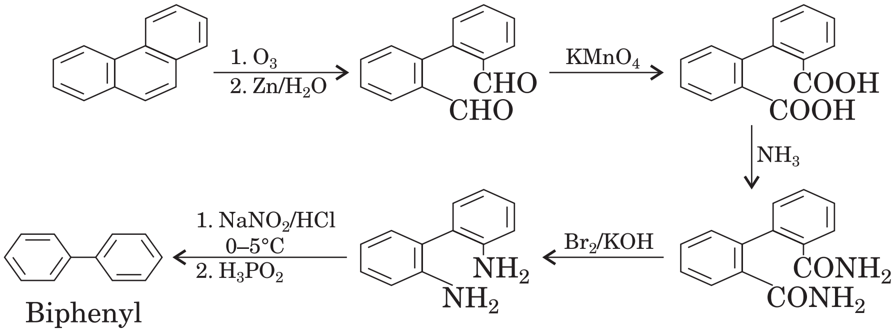
(c) 

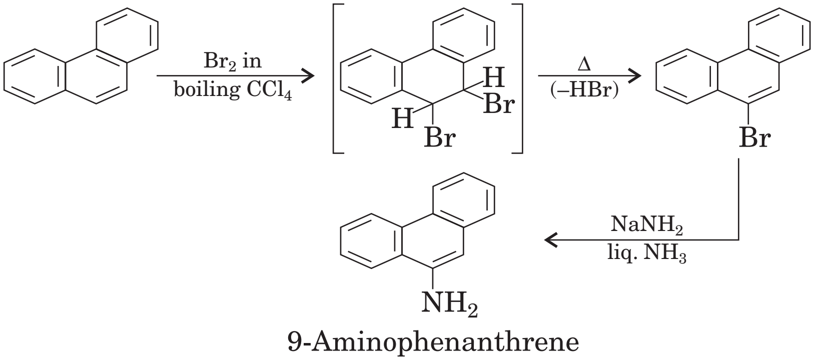
(d) 

(e) 

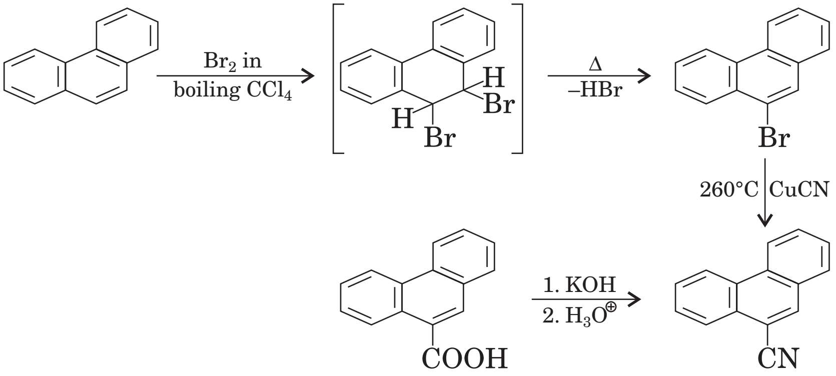
Solution

(a) 

(b) 

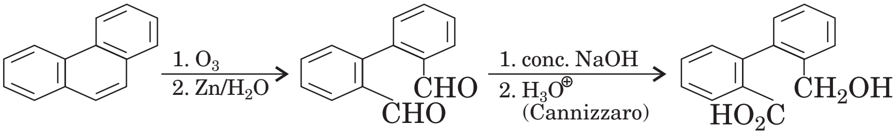
(c) 

(d)



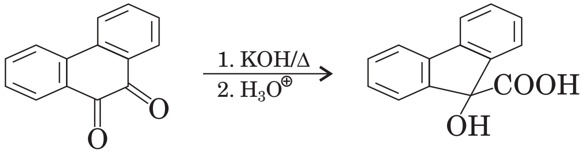
Phenanthrene-9-carboxylic acid

(e)

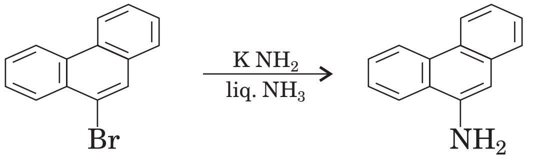


20. Give a curved-arrow mechanism for each of the following reactions:

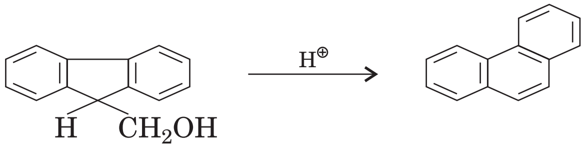
(a)



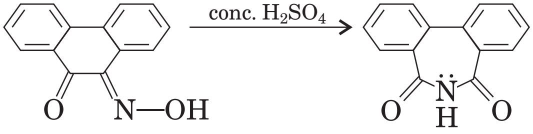
(b)



(c)

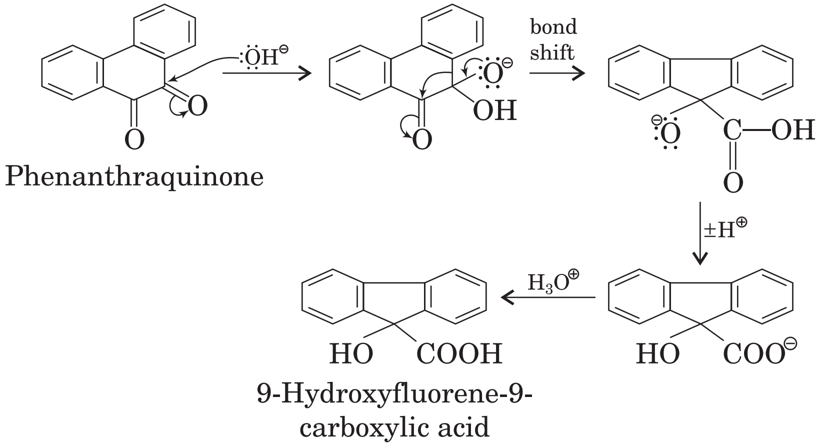


(d)

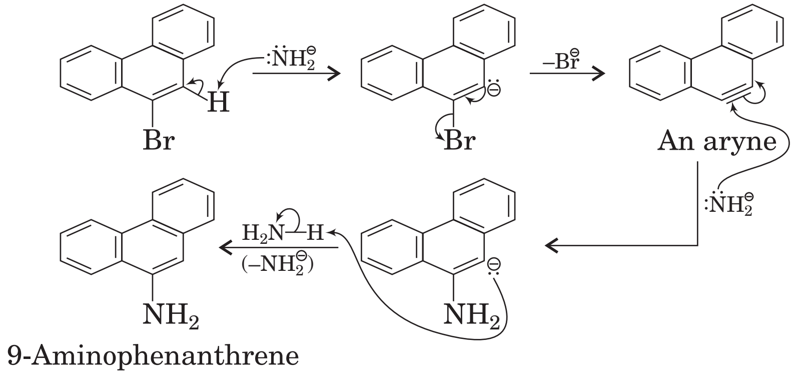


Solution

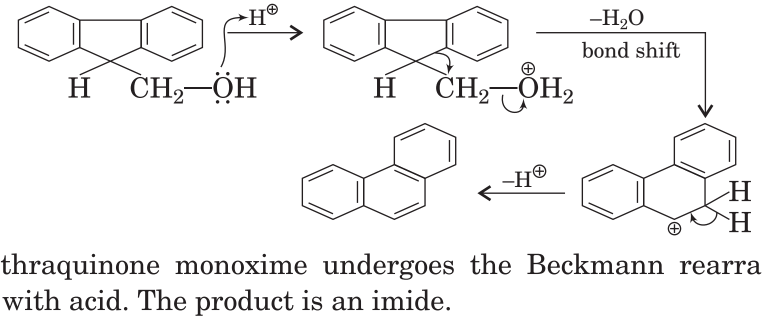
(a) When phenanthraquinone is warmed with alkali, it undergoes the benzilic acid rearrangement to form, after acidification, 9-hydroxyfluorene-9-carboxylic acid.



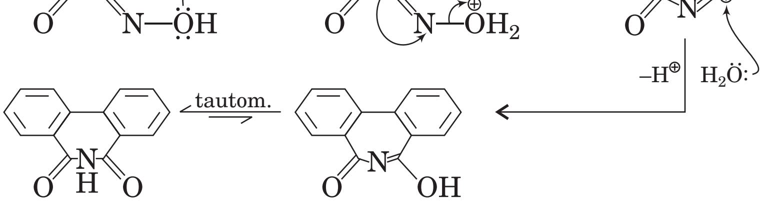
(b) The reaction proceeds through an aryne intermediate as follows:



(c) This is a case of dehydrative rearrangement which takes place as follows:

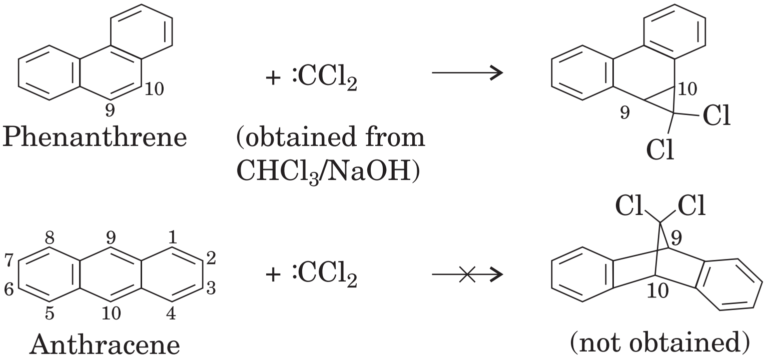


(d) Phenanthraquinone monoxime undergoes the Beckmann rearrangement when treated with acid. The product is an imide.



21. Explain why phenanthrene undergoes electrophilic addition of dichlorocarbene (:CCl_2) in it C-9/C-10 position but anthracene does not.

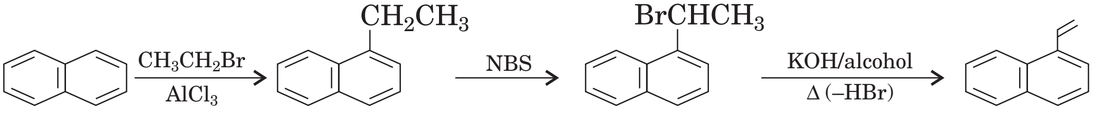
Solution C-9/C-10 positions are the reactive centres in both the isomeric anthracene and phenanthrene. In phenanthrene, C-9/C-10 positions are in adjacent positions, whereas in anthracene they are in *para* positions in the middle ring. Carbenes add to a double bond to form a cyclopropane ring system but cannot form higher carbocyclic ring systems. Because of this phenanthrene reacts with dichlorocarbene to form a cyclopropane derivative but anthracene does not.



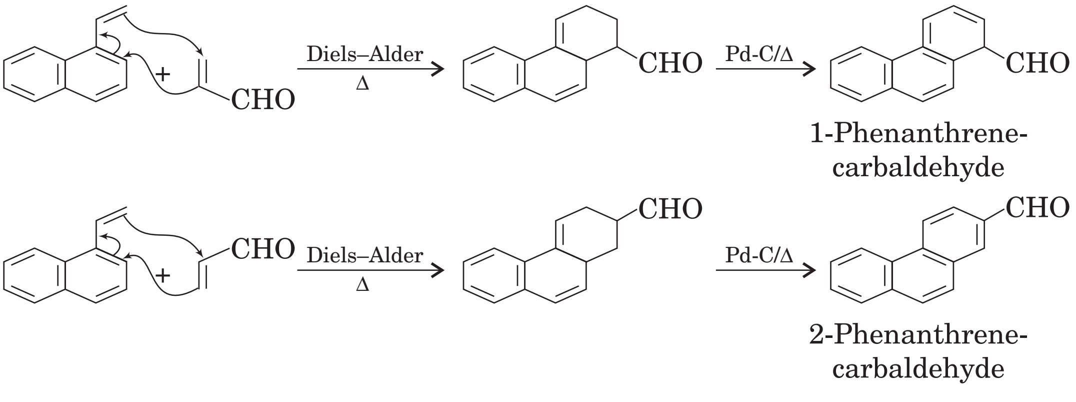
22. Synthesize 1-, 2-, 3- and 4-phenanthrenecarbaldehyde from naphthalene, 1-propanol and any compound containing two carbon atoms and using the Diels–Alder reaction in one of the steps.

Solution

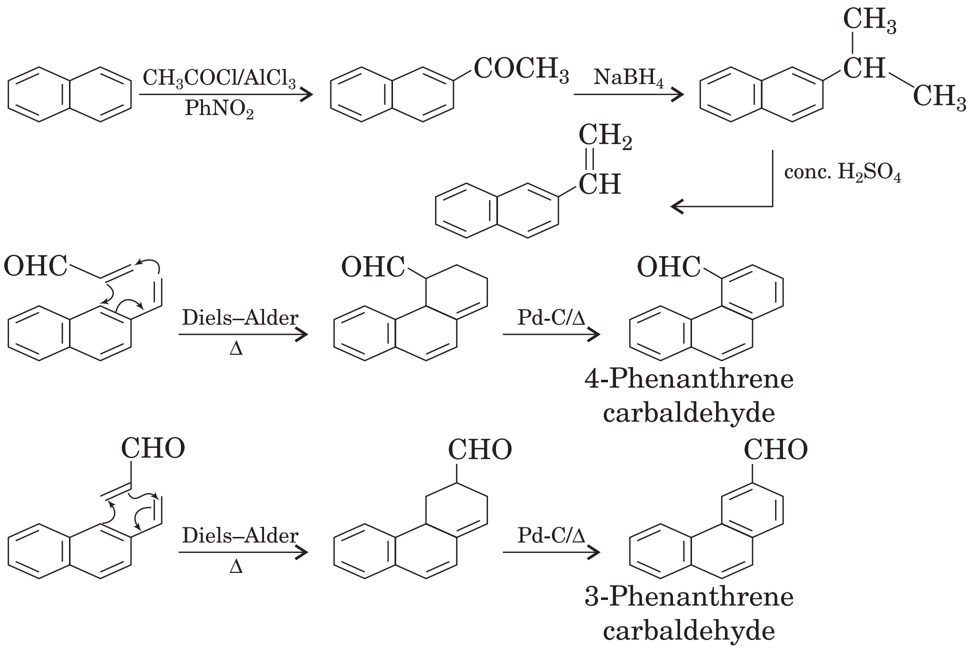
(i) Synthesis of 1- and 2-phenanthrenecarbaldehyde



$$CH_3CH_2CH_2OH \xrightarrow[\Delta]{Conc \cdot H_2SO_4} CH_3CH{=}CH_2 \xrightarrow{NBS} BrCH_2CH{=}CH_2 \xrightarrow[HCO_3^{\ominus}]{Me_2SO} CH_2{=}CHCHO$$



(ii) Synthesis of 3- and 4-phenenthrenecarbaldehyde



4-Phenanthrene carbaldehyde

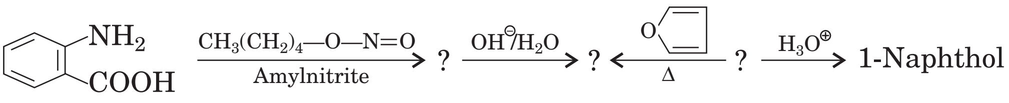
3-Phenanthrene carbaldehyde

23. Comment on the ability of anthracene, phenanthrene, naphthalene and benzene to act as dienes in the Diels-Alder reaction.

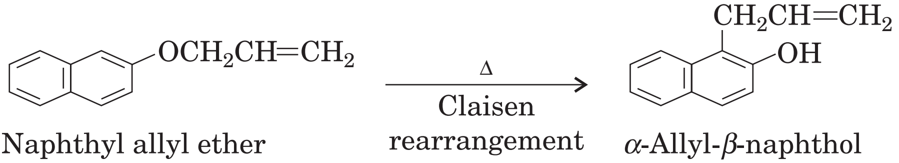
Solution Although anthracene readily participate as a diene in Diels-Alder reaction, phenanthrene does not. This can be explained in terms of the aromatic stability of the resulting adduct. If the central ring of phenanthrene reacted as does the central ring of anthracene, the aromaticity of all three rings would be destroyed. If the diene system of phenanthrene were to be included C-9═C-10 double bond, the aromaticity of two rings would be lost. The $\Delta G^{\ddagger}$ of such a reaction is much unfavourable. Naphthalene resists losing resonance energy and so it does not react under typical condition. However, it has been made to react under very high pressure. The aromatic ring of benzene is too stable and so it does not react.

STUDY PROBLEMS

1. Give Haworth synthesis of the following compounds:
   (a) 1,7-Dimethylnaphthyl
   (b) 7-Bromo-1-methylnaphthalene
   (c) 1-Ethynylnaphthalene
2. Predict the product and suggest the mechanism involved in each step of the following reaction sequence:

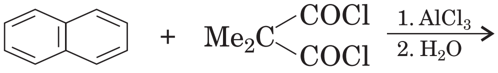


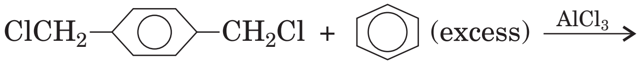
3. Which one of the C-1—C-2 and C-2—C-3 bonds in naphthalene is shorter in length? Use a resonance argument to explain your answer.
4. When β-naphthyl allyl ether is heated, it undergoes *ortho*-Claisen rearrangement where the allyl group migrates to C-1 and not to C-3. Explain this observation.

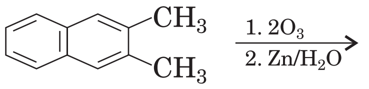


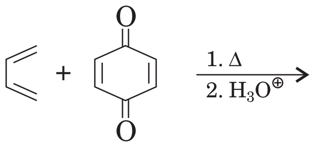
β-Naphthyl allyl ether α-Allyl-β-naphthol

5. Give the structures of the principal organic product(s) expected in each of the following reactions:

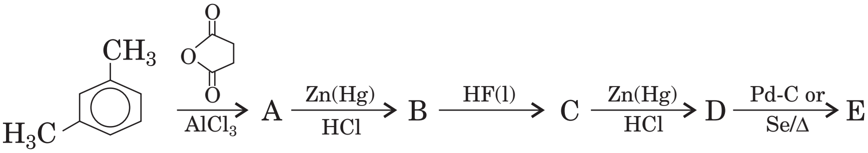
(a) 

(b) 

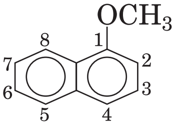
(c) 

(d) 

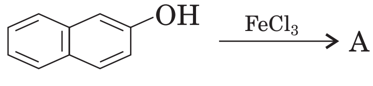
6. Give evidence in favour of the following statements:
   - (a) C═C bonds in naphthalene are somewhat fixed.
   - (b) Naphthalene is a bicyclic compound.
   - (c) Naphthalene is less aromatic than benzene.
7. Offer a suitable explanation for each of the following observations:
   - (a) In Haworth synthesis, the Clemmensen reduction of the keto acid is essential before cyclization.
   - (b) Nitration of 2-methylnaphthalene gives 2-methyl-1-nitronaphthalene as a major product whereas sulphonation of this compound affords 6-methylnaphthlene-2-sulphonic acid.
   - (c) When α-tetralone is heated with a 1:1 mixture of NaOH–KOH at 220°C, naphthalene is obtained.
8. Identify the compounds A–E in the following sequence of reactions:



9. How will you prepare α- and β-naphthols? Comment upon the coupling reactions of these two compounds.
10. Would 1-methoxynaphthalene nitrate more rapidly or more slowly than naphthalene at (a) C-4; (b) C-5; (c) C-6? Give your reasoning.

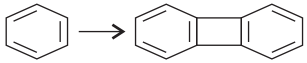


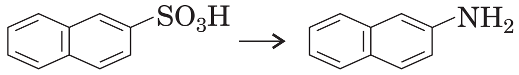
11. Predict the structure of the product A. Is it resolvable? Give your reasoning.

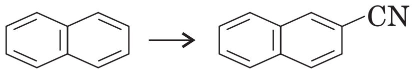


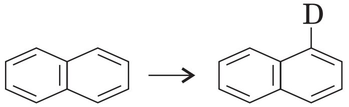
β-Naphthol

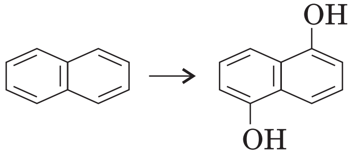
12. Suggest a synthetic sequence for each of the following conversion:

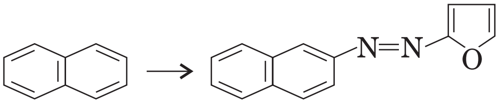
(a) 

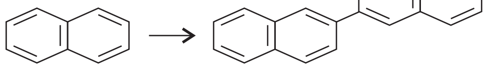
(b) 

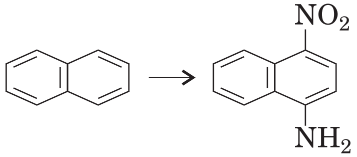
(c) 

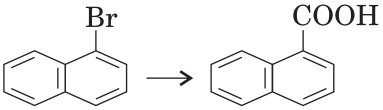
(d) 

(e) 

(f) 

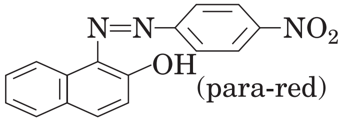
(g) 

(h) 

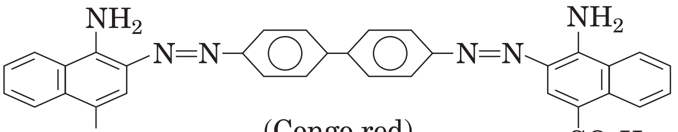
(i) 

13. (a) What is called para-red? How can it be prepared from β-naphthol? Mention one use of the reaction involved.

(b) How would you prepare *congo red* from naphthionic acid? Mention one use of Congo red. What is its colour in alkaline or acid solution?

[**Hint:** (a) 

(para-red)

(b) 

(Congo red)

14. Which one out of naphthalene and benzene is relatively more reactive in electrophilic aromatic substitution reactions and why?

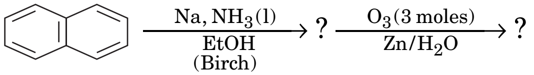
[**Hint:** The loss of aromaticity in one ring of naphthalene is equal to (255 – 151) kJ/mol or 104 kJ/mol. It is much less than for the loss of the single ring in benzene (151 kJ/mol)]

15. Explain why 2-naphthalenesulphonic acid is thermodynamically more stable than 1-naphthalenesulphonic acid. Devise an experiment to confirm the relative stabilities.

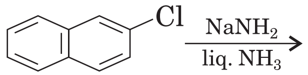
[**Hint:** When 1-naphthalenesulphonic acid is subjected to the same reaction conditions (conc. H_2SO_4/160°C), the same equilibrium mixture (≈85% of 2-acid plus ≃ 15% of l-acid) is obtained.]

16. Explain why bromination of benzene requires a Lewis acid catalyst but that of naphthalene requires no catalyst like $FeBr_3$.

17. Identify the products:

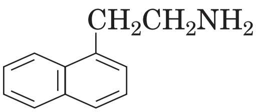


18. Predict the product and give a curved-arrow mechanism for the following reaction:

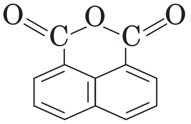


19. How would you synthesize the following compounds from naphthalene?

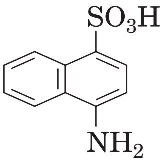
(a)



(b)



(c)



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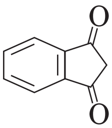

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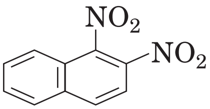

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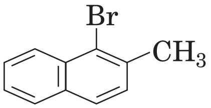
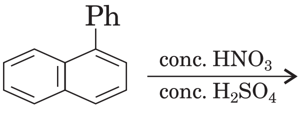


20. Predict the product and suggest a mechanism for each of the following reactions:

(a)



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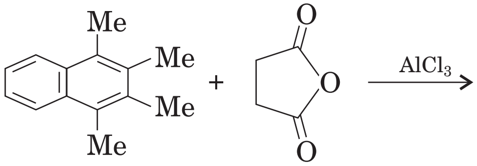
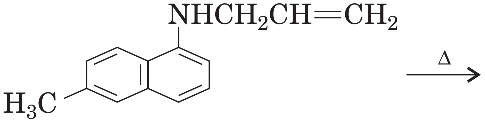
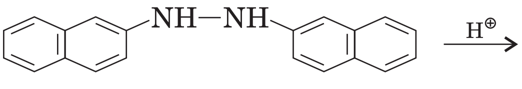


(c)



(d)



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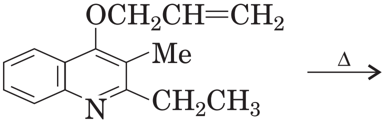

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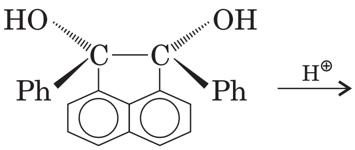

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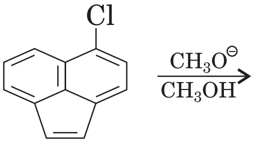
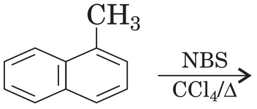
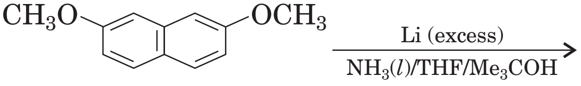


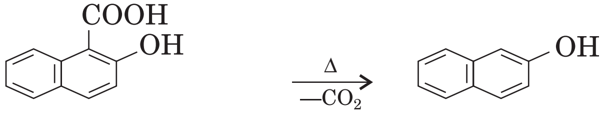
(h)



(i)

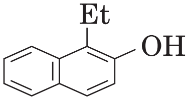


21. Offer a mechanistic explanation for the following observation:

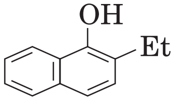


2-Hydroxy-1-naphthoic acid β-Naphthol

22. Which one of the following two naphthols will react with benzenediazonium chloride under basic condition to give an azo dye? Give reasons.



1-Ethyl-2-naphthol

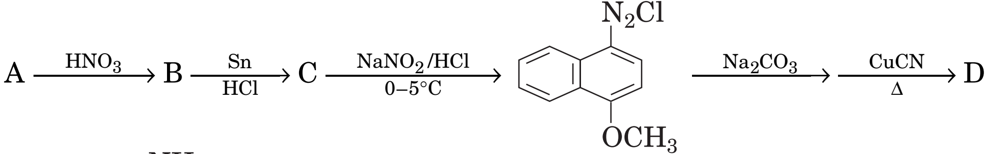


2-Ethyl-1-naphthol

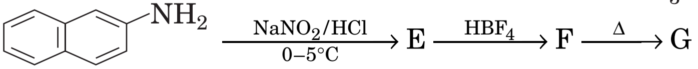
23. Explain why V_2O_5 catalyzed oxidation of naphthalene and 1-naphthylamine give the same product. Identify the product. What product do you expect to be formed when 1-nitronaphthalene is similarly oxidized?

24. Give structures for the compounds A–K:

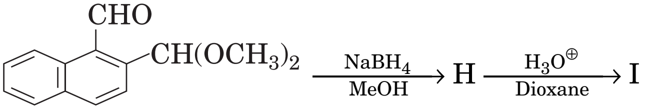
(a)



(b)



(c)



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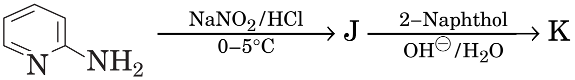
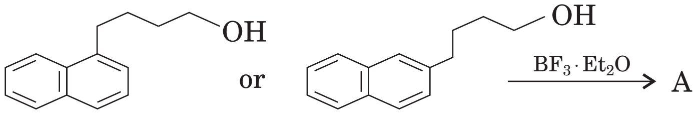
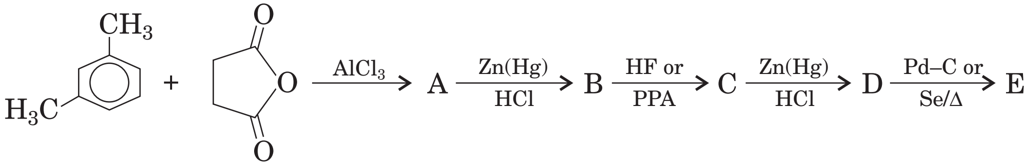


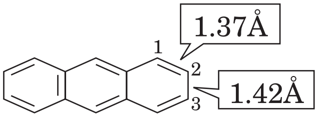
25. The same compound is obtained when either of the following two alcohols is treated with boron trifluoride etherate. Propose a structure for the product (A) and write a mechanism for its formation.



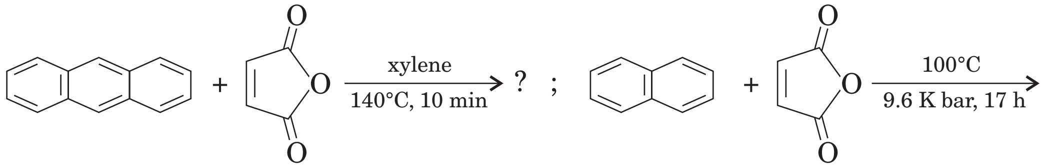
26. Identify the products A–E in the following sequence of reactions:



27. Explain why the 1,2—bond of anthracene is shorter than the 2,3—bond.



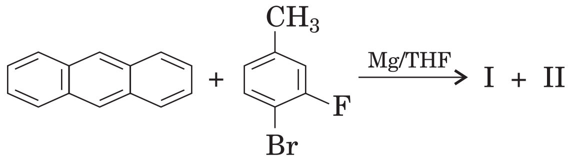
28. Although naphthalene and anthracene are aromatic hydrocarbons, they undergo the Diels–Alder reaction. For example, anthracene reacts readily with maleic anhydride to give an adduct. However, the reaction of naphthalene with maleic anhydride proceeds efficiently only under high pressure.



(a) Write down the structures of the adducts.
(b) Explain why anthracene is so much more reactive than naphthalene in the Diels–Alder reaction.

[**Hint:** Resonance energies of naphthalene and anthracene are 61 kcal/mol and 84 kcal/mol respectively.]

29. Predict the products (I and II) and give a curved-arrow mechanism for the following reaction:



Comment on the optical activity of the products and give your reasoning.

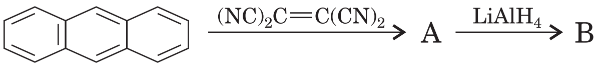
30. When 9,10-dihydroanthracene is refluxed in $NaOCD_3/CH_3OD$ for several hours and then recovered, the isolated compound is found to be identical with the starting material. However, anthrone rapidly exchanges its methylene protons for deuterons under the same conditions. Account for this difference.

[**Hint:** The structure of the intermediate anion is to be considered.]

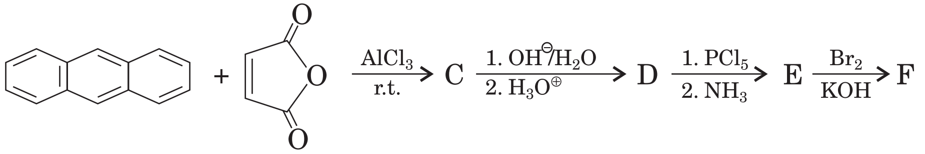
31. How would you prepare 2,9-dimethylanthracene starting with compounds containing one benzene ring?

32. Identify the products (A–F) in each of the following reaction sequences:

(a)



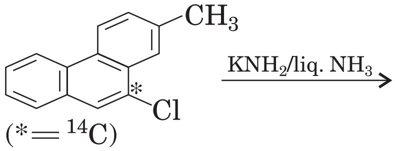
(b)



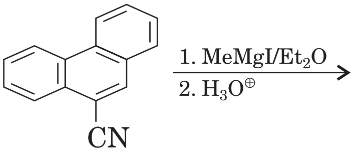
33. (a) The boiling point of anthracene (216°C) is much higher than that of phenanthrene (99°C), even though they are isomeric hydrocarbons. Explain.
(b) The resonance energy of anthracene is 84 kcal/mol. Is it more aromatic than benzene having resonance energy 36 kcal/mol?

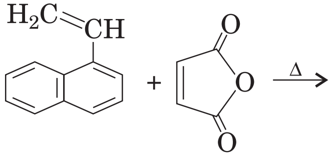
34. **Predict the product(s) and suggest a mechanism for each of the following reactions:**

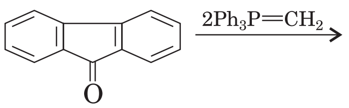
(a)

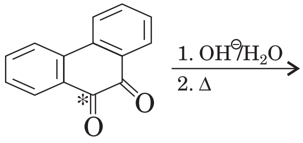


(b)



(c) 

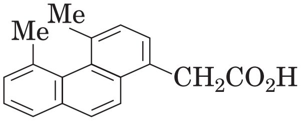
(d) 

(e) 

(*$=^{14}$C)

35. Anthracene can undergo the Diels-Alder reaction, whereas phenanthrene does not. Explain.
[**Hint:** Loss of RE is much greater in the case of phenanthrene compared to anthracene.]

36. Explain why the following compound is resolvable.



[**Hint:** The phenanthrene nucleus is planar and substituents lie in the plane. If, however, fairly large groups are in positions 4 and 5, there will not be enough room to accommodate both groups in the plane of the nucleus. Such a molecule (as shown above) will not be planar, and hence is asymmetric (due to bending of substituent bonds and buckling of the molecule as a whole) and consequently should be resolvable.]

37. How can *o*- and *m*-phenylenediamine be distinguished by reacting with phenanthraquinone?

38. Offer structures of the most suitable starting materials for the syntheses of the following compounds by the method mentioned:

(a)	6,7-Dimethylphenanthrene	(Haworth synthesis)
(b)	3,7-Dimethylphenanthrene	(Bardhan–Sengupta method)
(c)	2-Phenyl-3-ethylphenanthrene	(Bogert–Cook method)
(d)	1,4-Dimethylphenanthrene	(Johnson method)
(e)	Phenanthrene	(Fittig reaction)

References

1. Finar, I. L. *Organic Chemistry*, Vol. 2; ELBS and Longman Group (5th edn.).
2. Donaldson, *The Chemistry and Technology of Naphthalene Compounds*; Arnold (1958).
3. Clar, *Polycyclic Hydrocarbons*, Academic Press, Vols. I and II.
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5. Barclay, L. R. C., in Olah, G. A. *Friedel-Crafts and Related Reactions*, Vol. 2; Wiley, NY. 1964.
6. Norman, R. O. C., *Principles of Organic Synthesis*; Methuen and Co. Ltd., London (1968).
7. House, H. O. Modern Synthetic reactions, Second Edition; Benjamin/Cummings.
8. Bruice, P. Y., *Organic Chemistry*, Third Edition; Pearson.

Heterocyclic Compounds

6

Chapter Outline

Introduction

6.1 Nomenclature of Heterocyclic Compounds

6.2 Five-membered Heterocyclic Compounds with One Heteroatom
  - 6.2.1 Pyrrole and Its Derivatives
  - 6.2.2 Furan and Its Derivatives
  - 6.2.3 Thiophene and Its Derivatives

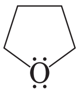
6.3 Six-membered Heterocyclic Compounds with One Heteroatom
  - 6.3.1 Pyridine and Its Derivatives
  - 6.3.2 Pyridine *N*-oxide

6.4 Benzo-fused Five- and Six-membered Heterocyclic Compounds with One Heteroatom
  - 6.4.1 Indole and Its Derivatives
  - 6.4.2 Quinoline and Its Derivatives
  - 6.4.3 Isoquinoline and Its Derivatives

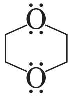
INTRODUCTION

Cyclic organic compounds are divided into two large classes: those having only carbon atoms in their rings are known as *carbocylic compounds* (e.g., cyclohexane) and those in which at least one atom other than carbon forms a part of the ring system are called *heterocyclic compounds* (Gk., heteros, other + cycle). Most of the heterocyclic compounds contain carbon atom along with heteroatom like oxygen, nitrogen and sulphur. Heterocyclic compounds occur so widely in nature and are of such importance chemically that any discussion of organic chemistry will not proceed very far without mentioning them. In fact, the heterocyclic derivatives represents nearly half of thirteen million chemical species discovered up to date. A large number of heterocyclic compounds are essential to life. Various compounds, such as alkaloids, vitamins, antibiotics, essential amino acids, nucleic acids, hormones and a large number of synthetic drugs contain heterocyclic ring systems. A good knowledge of heterocyclic chemistry is, therefore, very much necessary of the organic chemists, in general.

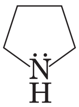
Heterocyclic compounds may be classified into *aliphatic* and *aromatic*. The aliphatic heterocycles are the cyclic analogues of ethers, amines, thioethers, amides, etc. Their properties are influenced particularly by the strain of the ring. These compounds generally consist of small (three- and four-membered) and common (five- to seven-membered) ring systems. On the other hand, the aromatic heterocyclic compounds are those which have at least one heteroatom in the ring and behave in a manner similar to benzene in some of their properties. Furthermore, these compounds obey the Huckel's rule, which states that cyclic conjugated planar systems containing $(4n + 1)\pi$ electrons are aromatic. The aromatic heterocycles possess considerable resonance energies. The heteroatom can play an extremely important role in determining the properties of compounds of this type. Examples of some aliphatic heterocyclic compounds are as follows:



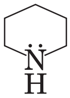
Tetrahydrofuran (THF)



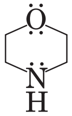
1,4-Dioxane



Pyrrolidine

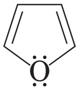


Piperidine

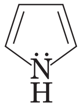


Morpholine

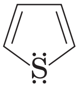
Examples of some aromatic heterocycles are as follows:



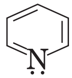
Furan



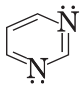
Pyrrole



Thiophene



Pyridine



Pyrimidine

6.1 NOMENCLATURE OF HETEROCYCLIC COMPOUNDS

Heterocyclic compounds are frequently named by their trivial names. Although they convey little or no structural information, they are still widely used. The systematic name (IUPAC), in contrast, is designed so that one can deduce from it the structure of the compound. The following is the systematic method of nomenclature:

(i) The size of a monocyclic ring from 3 to 10 is indicated by a stem : 3, ir (t*ri*) ; 4, et (t*et*ra) ; 5, ol ; 6, in; 7, ep (h*ep*ta) ; 8, oc (*oc*ta) ; 9, on (n*on*a) and 10, ec (d*ec*a).

(ii) The names of monocyclic compounds are derived by a prefix (or prefixes) indicating the nature of the heteroatom present, and eliding 'a' where necessary, e.g., *oxa* for oxygen, *thia* for sulphur, *aza* for nitrogen, *sila* for silicon, etc. When two or more of the same heteroatoms are present, the prefixes di, tri, etc. are used, e.g., dioxa, triaza, etc. If the ring contains different heteroatoms, their order of citation starts with the heteroatom of as high a group in the periodic table and as low an atomic number in that group. Therefore, the order of naming will be O, S, N, P, Si, etc. For instance, a heterocycle containing one oxygen and one nitrogen atom will be referred to as *oxaza*, whereas *thiaza* denotes a heterocycle containing one S and one N atom.

(iii) Numbering of the ring starts with the heteroatom and proceeds to give substituents or the other heteroatoms of the lowest numbers possible. If the heteroatoms are different, then numbering starts at the atom cited first according to the rule in (ii) and proceeds round the ring in order of precedence.

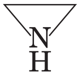
(iv) The degree of unsaturation in the ring is indicated by putting an appropriate suffix. These suffixes change to some extent according to whether or not the ring containing nitrogen. Suffixes for three- to six-membered rings are listed in the following table.

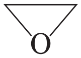
Suffixes of some simple heterocyclic compounds

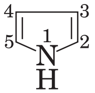
No. of members in the ring	Rings containing nitrogen		Rings containing no nitrogen	
	Unsaturated	Saturated	Unsaturated	Saturated
3	–irine	–iridine	–irene	–irane
4	–etc	–etidine	–ete	–etane
5	–ole	–olidine	–ole	–olane
6	–ine	*	–in	–ane

*Expressed by prefixing ‘perhydro’ to the name of the corresponding unsaturated compound.

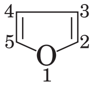
Some simple examples are given below with their trivial names as well as IUPAC names (in parentheses). It is to be noted that when the name contains two vowels coming together, then ‘a’ of the prefix is omitted (e.g., oxirane is to be written instead of oxairane).


Ethylene imine
(Aziridine)

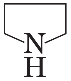

Ethylene oxide
(Oxirane)

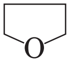


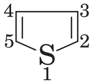
Pyrrole
(Azole)



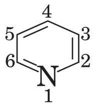
Furan
(Oxole)


Pyrrolidine
(Azolidine)

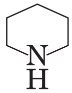

Tetrahydrofuran
(Oxolane)

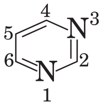


Thiophene
(Thiole)

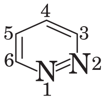


Pyridine

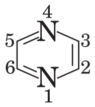

Piperidine
(Perhydroazine)



Pyrimidine
(1,3-Diazine)

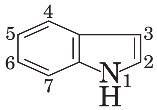


Pyridazine
(1,2-Diazine)

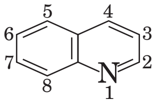


Pyrazine
(1,4-Diazine)

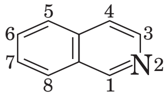
Common names of some benzo-fused heterocycles are given below:



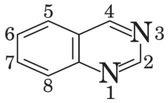
Indole



Quinoline



Isoquinoline

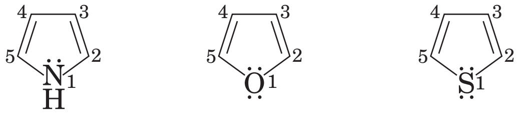


Quinazoline

In isoquinoline, a carbon atom has a lower number than the nitrogen atom to preserve an orderly sequence around the peiphery of the two rings.

6.2 FIVE-MEMBERED HETEROCYCLIC COMPOUNDS WITH ONE HETEROATOM

Pyrrole, furan and thiophene are the simplest five-membered heterocyclic compounds containing a single heteroatom.

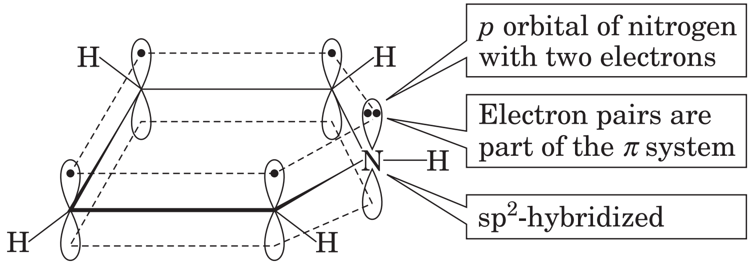


Pyrrole Furan Thiophene

Some general characteristics of these simple heterocycles are discussed below:

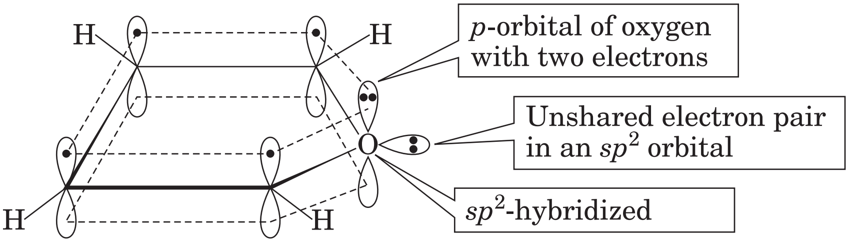
1. Structure

Pyrrole The nitrogen atom and the four carbon atoms in pyrrole are sp^2-hybridized and all of them adopt a trigonal planar geometry. The three sp^2 orbitals of nitrogen contain one electron each and the p-orbital contains a pair of electrons. The sp^2 orbitals make two N—C bonds (sp^2–sp^2) and one N–H (sp^2–s) bond. The N—H bond lies in the plane of the ring. The p orbitals of carbon also carry one electron each. The five p-orbitals (four of C and one of N) being in the same plane, overlap to give a total of six π-electrons, thus resulting in an aromatic sextet in accordance with the Huckel's rule [$(4n + 2)\pi$ electrons, where n = 1].


H
H
H
H
N
H
p orbital of nitrogen with two electrons
Electron pairs are part of the π system
sp2-hybridized

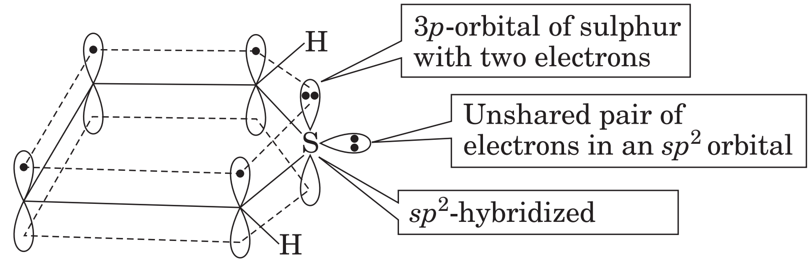
Orbital picture of pyrrole

Furan The oxygen atom and the four carbon atoms in furan are sp^2-hybridized and all of them adopt a trigonal planar geometry. Out of the three sp^2 hybrid orbitals of oxygen, two containing one electron each are utilized in making two O—C σ bonds (sp^2—sp^2) and the third carries an unshared pair of electrons, which does not take part in bond formation. It lies in the plane of the ring but is directed away from it. The p-orbital contains a pair of electrons. The p_z-orbital of each carbon also carry one electron. The five p-orbitals (four of C and one of O) being in the same plane, overlap to give a total of six π-electrons, thus resulting in an aromatic sextet in accordance with the Huckel's rule [$(4n + 2)$ π electrons, where n = 1].


H
H
p-orbital of oxygen with two electrons
O
Unshared electron pair in an sp2 orbital
H
H
sp2-hybridized

Orbital picture of furan

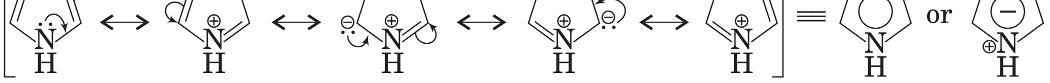
Thiophene The sulphur atom and the four carbon atoms in thiophene are sp^2-hybridized and like pyrrole and furan it is a planar cyclic molecule with six π-electrons. Each carbon atom contributes one π-electron and the sulphur atom provides the other two. The basic structure is made up of five sp^2-sp^2 σ bonds. The six π-electrons form an aromatic sextet in accordance with the Huckel's rule. However, unlike oxygen, sulphur provides 3p-orbitals to overlap with 2p-orbitals of carbon to form the aromatic sextet.


H
3p-orbital of sulphur with two electrons
S
Unshared pair of electrons in an sp2 orbital
sp2-hybridized
H

Orbital picture of thiophene

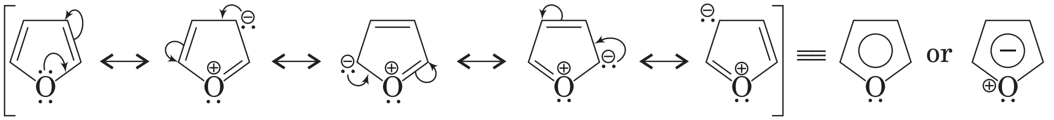
These three heterocycles are considered to be π-excessive, i.e., rich in electrons because the five sp^2-hybridized atoms sustain a 6π-electron system. In other words, there are six electrons in five orbitals.

2. Aromatic character These heterocycles exhibit some amount of aromatic character, i.e., these are aromatic heterocycles, because they obey the Huckel's rule of aromaticity. All of them have planar closed ring of six π-electrons where the sp^2-hybridized heteroatom in each case provides a lone pair of electrons from its p-orbital. All of them can be represented by resonance hybrid structures. These are shown as follows.

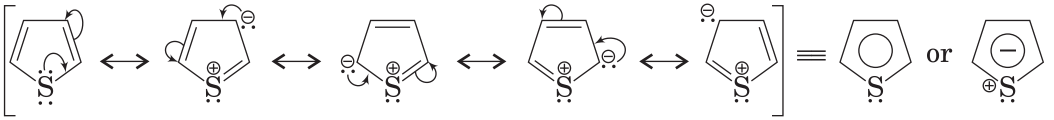


Resonance structures of pyrrole

Hybrid structure

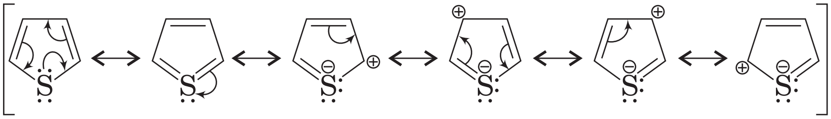


Resonance structures of furan Hybrid structure

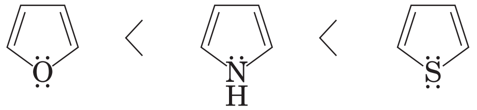


Resonance structures of thiophene Hybrid structure

It is to be noted that sulphur can also use 3*d* orbitals (oxygen and nitrogen cannot) in electron delocalization. Hence, more canonicals are possible for thiophene than for furan and pyrrole.



The order of increasing aromaticity of these three five-membered heterocycles is as follows:



	Furan	Pyrrole	Thiophene
Resonance Energy (kcal/mol):	16	22	29

Since oxygen is more electronegative than nitrogen and sulphur, the oxygen atom in furan is much reluctant to release its electrons into the ring to form the sextet of π-electrons [$(4n + 2)\pi$, where $n = 1$] required for aromaticity and as a consequence, furan is least aromatic of the three. Again, since sulphur is less electronegative than nitrogen and oxygen, the sulphur atom in thiophene is more willing to rease electrons into the ring to maintain aromaticity. Besides, sulphur atom utilizes its 3*d*-orbital in resonance process (oxygen and nitrogen cannot) giving rise to a greater number of resonance structures, thus making the thiophene molecule more aromatic in comparison to furan and pyrrole. Pyrrole has intermediate aromaticity because nitrogen is less electronegative than oxygen but more electronegative than sulphur.

Evidence in favour of aromatic character

(i) These heterocycles undergo electrophilic substitution reactions (e.g., nitration, halogenation, etc.) like benzene and naphthalene rather than addition reactions.

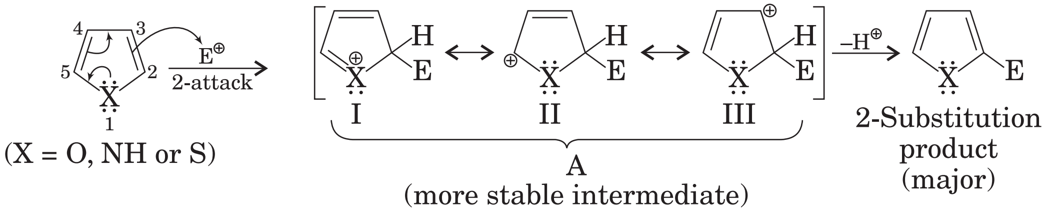
(ii) They show the effect of ring current in their n.m.r. spectra.

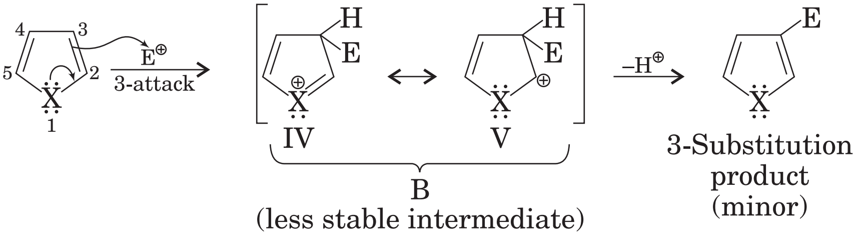
(iii) Heats of combustion of these heterocycles indicate resonance stabilization to the extent of 16 kcal/mol for furan, 22 kcal/mol for pyrrole and 29 kcal/mol for thiophene, which are greater in magnitude than the conjugated dienes (~4 kcal/mol).

(iv) Their aromatic character is further recognized from a comparison of dipole moments measured for these compounds and their tetrahydro derivatives.

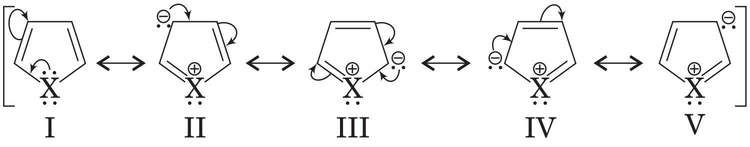
3. Electrophilic Substitution Pyrrole, furan and thiophene are more reactive than benzene towards electrophilic aromatic substitution. In these three heterocycles, the electron density on each of the carbons is increased due to delocalization of the nonbonding pair of electrons on the heteroatom (N, O and S) onto the ring carbon atoms. Since the rate determining step of an electrophilic substitution reaction involves attachment of the electrophile to the aromatic ring carbon, increasing the electron density of the ring carbons increases the rate of electrophilic substitution of these three heterocycles.

Since these heterocycles have two non-equivalent positions (C-2 and C-3), the electrophilic substitution is expected to take place at these two positions. In fact, the substitution reaction occurs preferentially at the 2-position. Both of the intermediate carbocations obtained by the electrophilic attack at C-2 and C-3 of pyrrole, furan or thiophene have a resonance structure (I and IV) in which all the atoms (except H) have complete octets. The intermediate A has two additional structures (II and III), whereas the intermediate B has one addition structure (V). Therefore, A has one more resonance structure than B. Again, each of the structures II and III has a positive charge on a relatively stable secondary allylic carbon, whereas the additional resonance structure V of the intermediate B has a positive charge on a secondary carbon which is not allylic. For these reasons, the intermediate A is relatively more stable than the intermediate B and because of this, electrophilic substitution of these three heterocycles occurs preferentially at the 2-position.



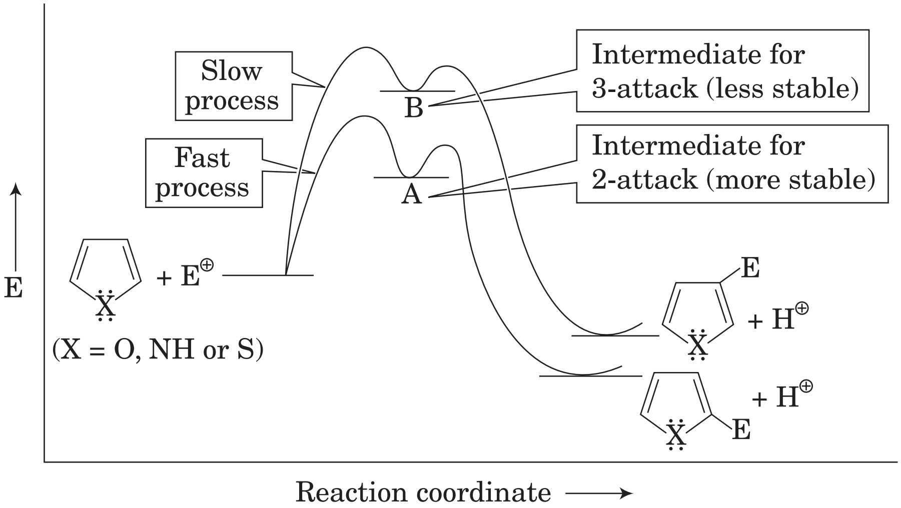


Like substituted benzenes this can also be explained simply by considering the resonance structures of these heterocycles.

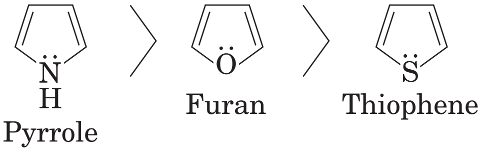


A resonance structure having two dissimilar charges close to each other is relatively more stable and more contributing than the structure in which the charges are further apart. Therefore, the structures III and IV with two adjacent charges are relatively more stable than the structures II and V and so they contribute much to the hybrid. Because of this, the resonance hybrid has a larger electron density at C-2 than at C-3. Hence, on the basis of charge distribution, the electrophilic substitution would be expected to take place preferentially at C-2 (or -5).

Energy diagram The energy profile diagram for the electrophilic substitution of the five-membered heterocycles is as follows:

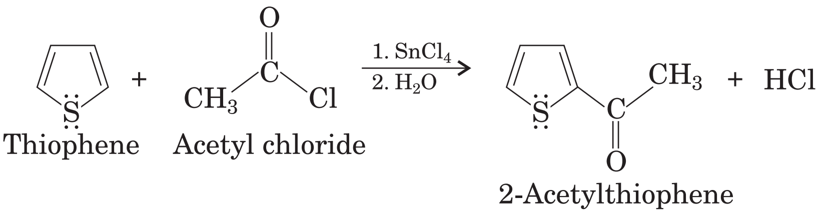


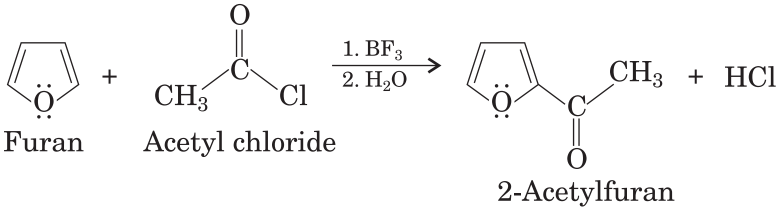
Order of reactivity The order of reactivity of these three heterocycles towards on electrophile, i.e., towards electrophilic aromatic substitution is as follows:

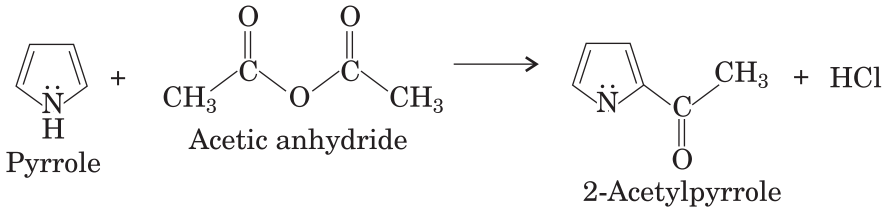


The oxygen atom in furan is more electronegative than the nitrogen atom in pyrrole and so, the oxygen atom is less willing to donate electrons into the ring compared to the nitrogen atom. For this reason, furan is less reactive than pyrrole towards electrophilic substitution reactions. Although the sulphur atom in thiophene is less electronegative than oxygen and nitrogen, yet it is less reactive and this is because *p* electrons of sulphur are in a 3*p*-orbital (larger in size), which overlaps less effectively than the 2*p*-orbital of oxygen or nitrogen with the 2*p*-orbital of carbon.

This order of reactivity can be proved by comparing the strength of the Lewis acid required to catalyse a Friedel–Crafts acylation reaction. The Friedel–Crafts acylation of thiophene can be carried out by using a weaker Lewis acid like $SnCl_4$. Furan requires BF_3, an even weaker Lewis acid. Pyrrole is so reactive that an anhydride is to be used instead of a more reactive acyl chloride and in fact, the reaction requires no Lewis acid catalyst.

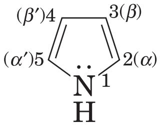






6.2.1 Pyrrole and Its Derivatives

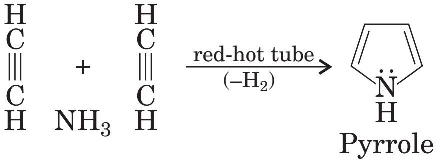
Pyrrole is a very important five-membered heterocyclic compound because its nucleus occurs in many natural compounds, e.g., alkaloids, chlorophyll, haematin, etc. It occurs in coal-tar and bone oil. Its isolation from bone oil involves washing the latter with dilute alkali to remove acidic substances, then with acid to remove strongly basic substances, and finally fractionating. Pyrrole distils over in the fraction boiling between 100 and 150°C. It is purified by fusing with KOH. Solid potassiopyrrole is obtained and this, on steam distillation, produces pure pyrrole (b.p. 131°C). The numbering of pyrrole commences from the nitrogen atom which is assigned position-1. The substituents may also be numbered by the Greek letters. There are two monosubstituted derivatives of pyrrole, 2(or α) and 3 (or β). The four possible disubstitution products are: 2,3 (α, β), 2,4 (α, β'), 2,5 (α, α') and 3,4 (β, β').



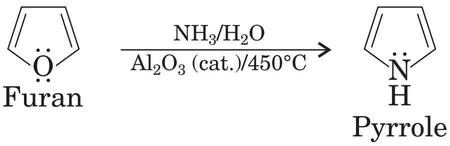
Pyrrole

6.2.1.1 Synthetic Methods

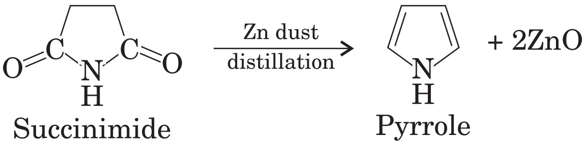
1. From acetylene Pyrrole may be synthesized by passing a mixture of acetylene and ammonia through a red-hot tube:



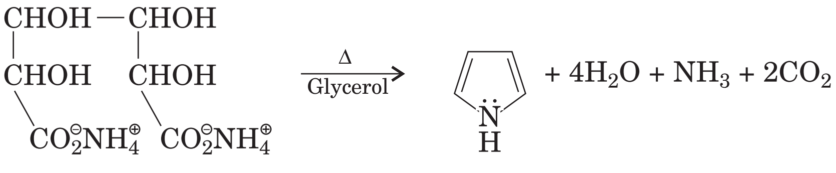
2. From furan Commercially pyrrole is obtained by passing a mixture of furan, ammonia and steam over heated aluminium oxide as catalyst.



3. From succinimide Succinimide on distillation with zinc dust gives pyrrole.

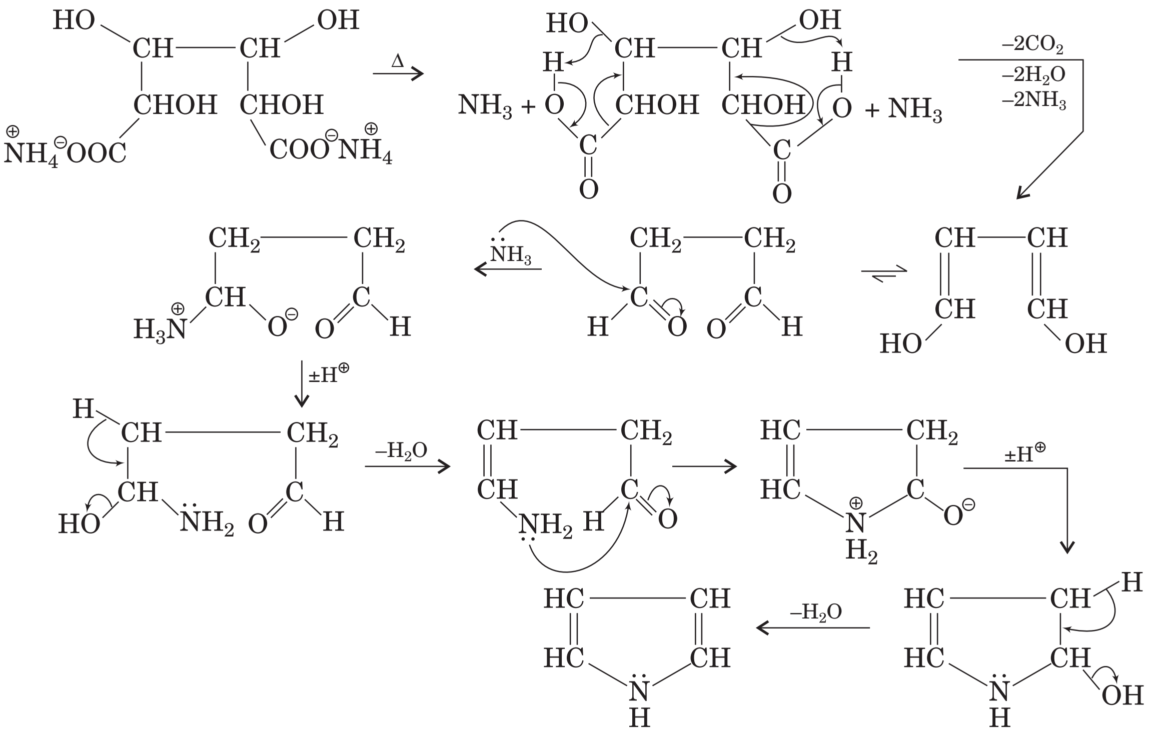


4. From ammonium mucate A convenient method to prepare pyrrole in the laboratory consists of heating ammonium mucate in glycerol at 200°C.

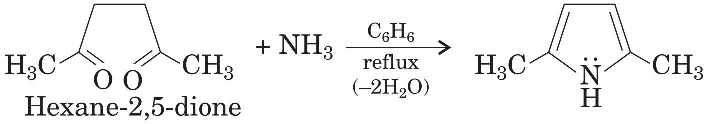

CHOH
CHOH
CHOH
CHOH
CO$_2^{\ominus}$NH$_4^{\oplus}$
CO$_2^{\ominus}$NH$_4^{\oplus}$
Δ
Glycerol
N
H
+ 4H$_2$O + NH$_3$ + 2CO$_2$

Ammonium mucate

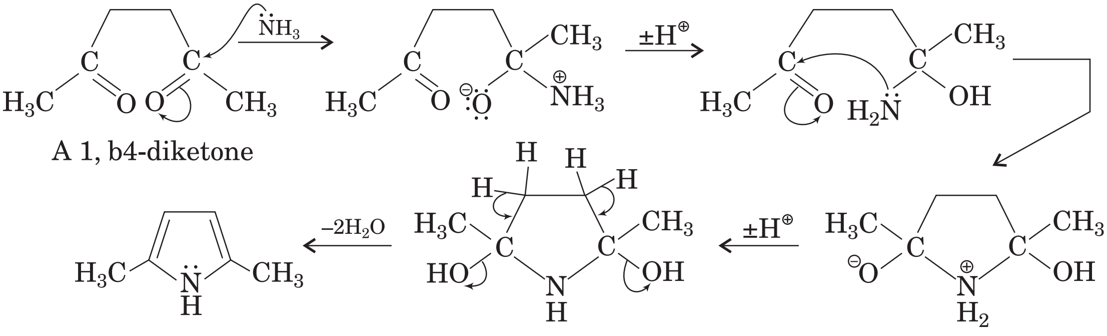
Mechanism of the reaction



5. Paal–Knorr synthesis The Paal–Knorr synthesis is the most general method for the synthesis of substituted pyrroles and this is carried out by heating a 1,4-diketone with ammonia (used as ammonium sulphate) or a primary amine. For example, 2,5-dimethylpyrrole can be prepared by allowing hexane-2,5-dione to react with ammonia.

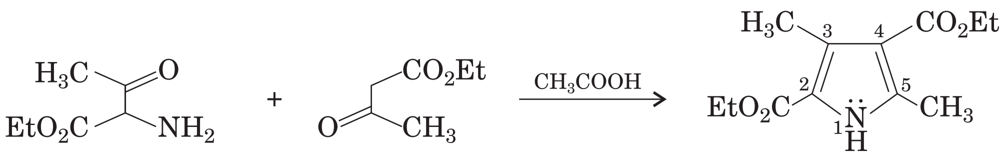


Mechanism of the reaction Successive nucleophilic addition of ammonia (or amine) nitrogen to the two carboxyl carbon atoms followed by the loss of two molar equivalents of water represent the net course of the synthesis.



Pyrrole may be prepared by using succinaldehyde ($OHCCH_2CH_2CHO$).

6. Knorr synthesis This is the most extensively used route for pyrrole synthesis. It involves condensation of an α-amino ketone with a β-keto ester or a β-diketone in the presence of acetic acid. Diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate, for example, can be prepared by this method by allowing ethyl 2-amino-3-oxobutanoate (an α-amino ketone) to react with ethyl acetoacetate (a β-keto ester).

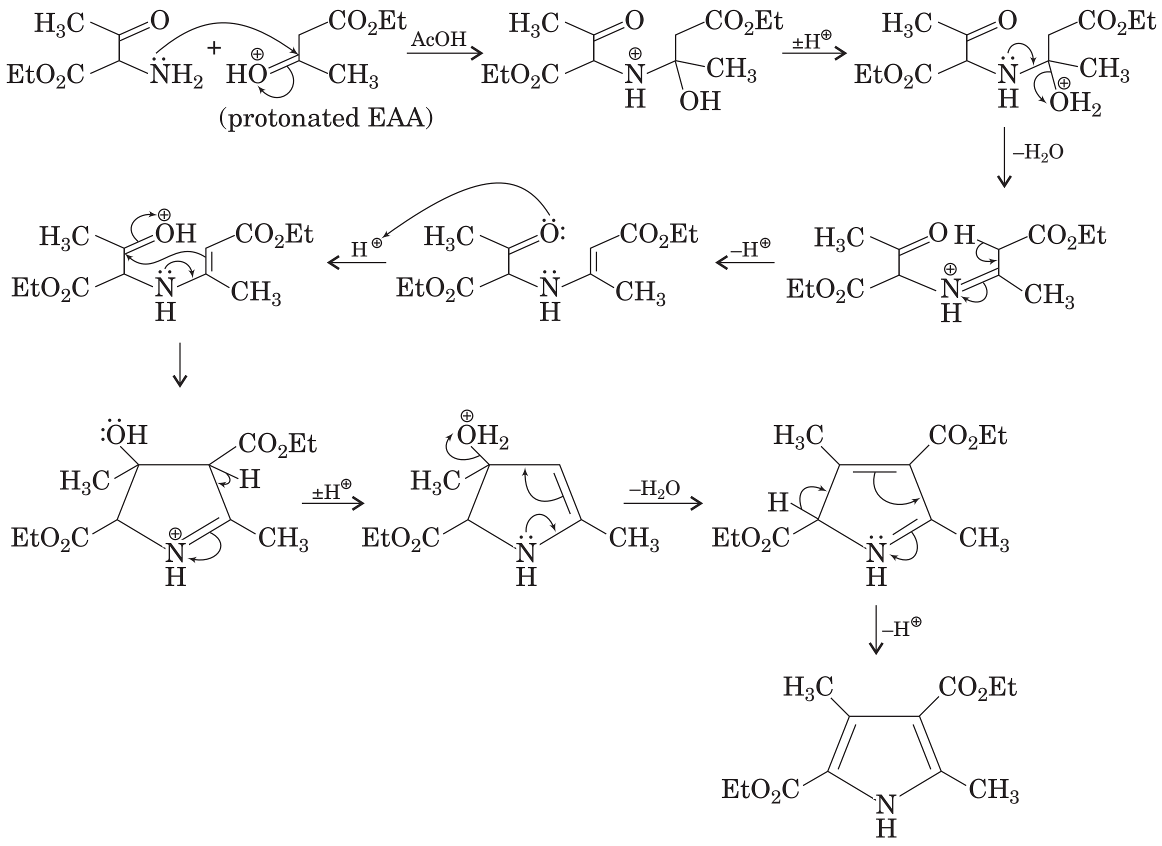


Ethyl 2-amino-3-oxobutanoate (an α-amino ketone)

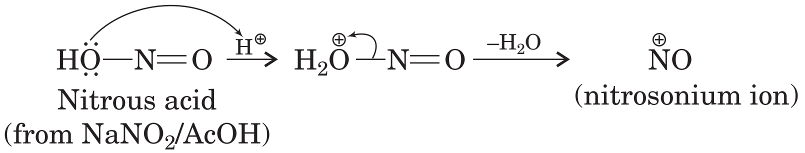
Ethyl acetoacetate (a β-keto ester)

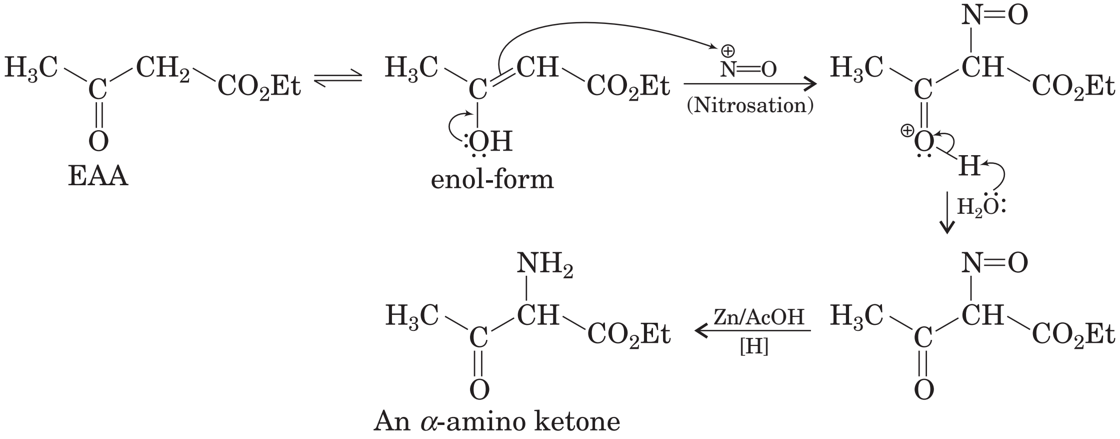
Diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate

Mechanism of the reaction:

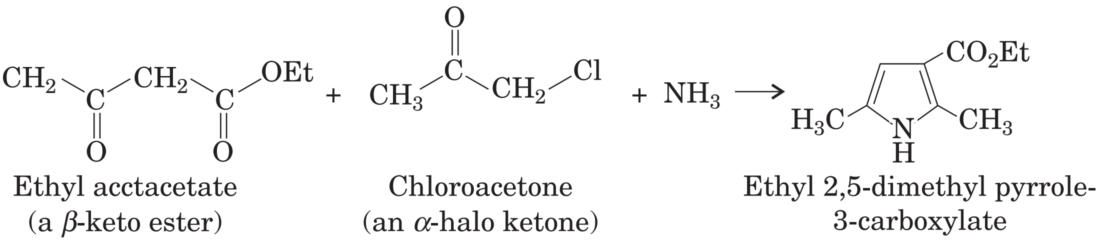


The α-amino ketone is, in fact, generated in the reaction medium by nitrosation of the same β-keto ester followed by reduction with Zn/AcOH.

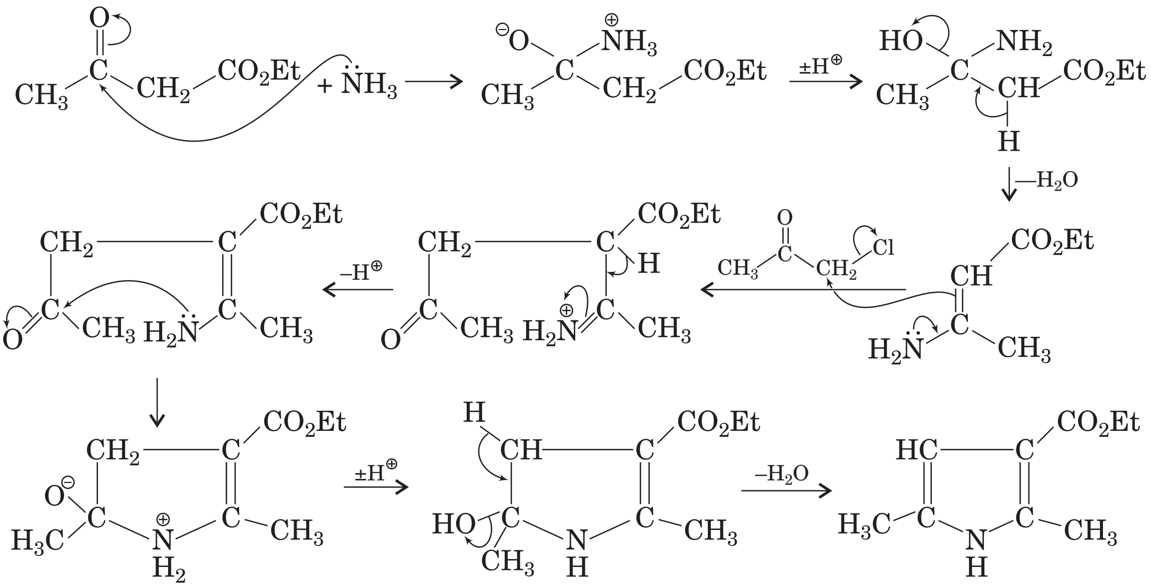




7. Hantzch synthesis This method involves condensation of an α-haloketone (or aldehyde) with a, β-keto ester in the presence of ammonia or a primary amine. 2,5-Dimethylpyrrole-3-carboxylate, for example, can be prepared by allowing ethyl acetoacetate to react with chloroacetone in the presence of ammonia.

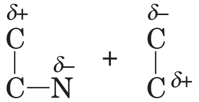


Mechanism of the reaction The reaction proceeds through the formation of an enamine, which displaces the chlorine of chloroacetone followed by cyclisation to yield the corresponding pyrrole derivative.

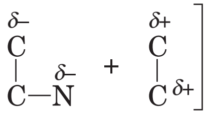


[It is to be noted that the *Knorr synthesis* and the *Hantzsch synthesis* are , in fact, carried out by combining the two aliphatic skeletal fragments (a) and (b), respectively.

(a)



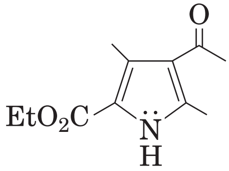
(b)



]

Synthesis of Some Pyrrole Derivatives (Target Molecules) through Disconnection Approach

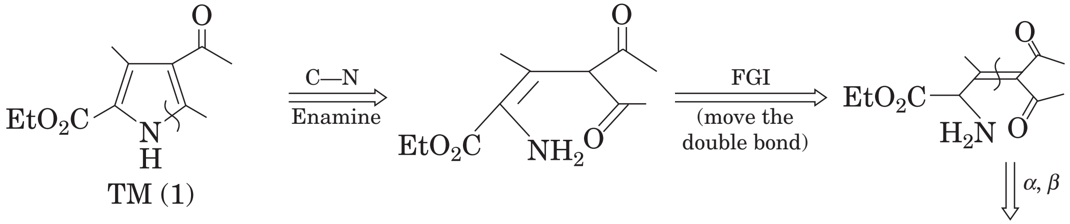
1.

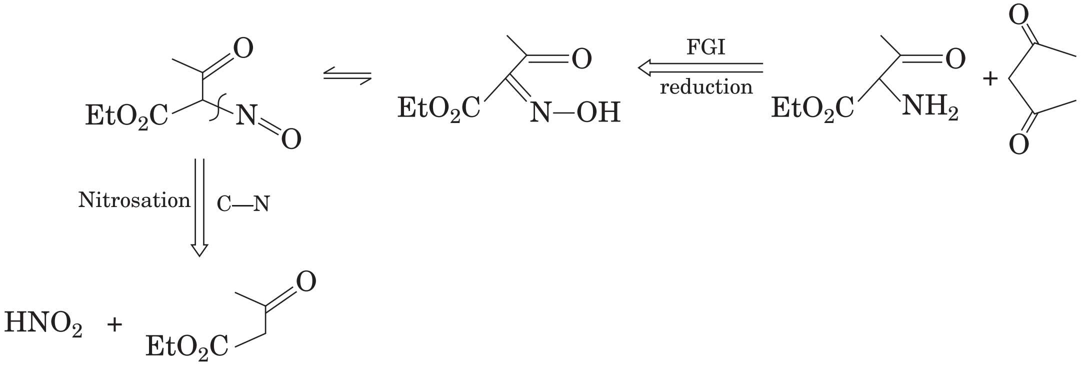


TM (1)

(Ethyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate)

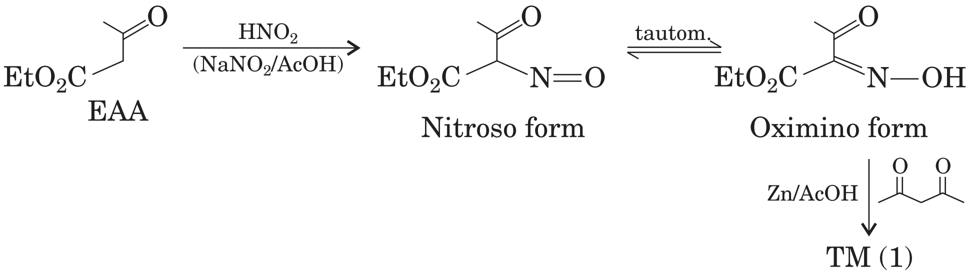
Retrosynthetic analysis



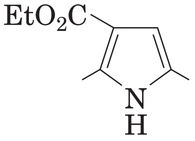


Knorr pyrrole synthesis involves condensation of a α-amino ketone with a β-keto ester or a β-diketone in the presence of acetic acid.

Synthesis



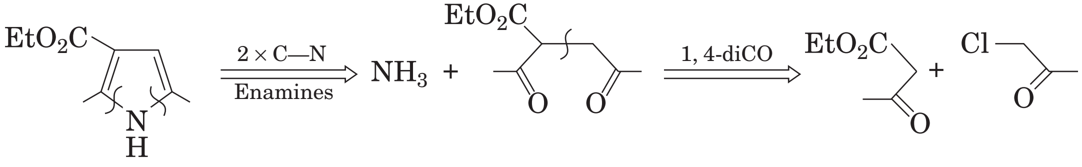
In the final step, the oximino tautomer undergoes reduction by Zn/AcOH to give an α-amino ketone which subsequently reacts with pentane-2,4-dione (a β-diketone) to yield the target molecule.

2. 

(Ethyl 2,5-dimethylpyrrole-3-carboxylate)

TM (2)

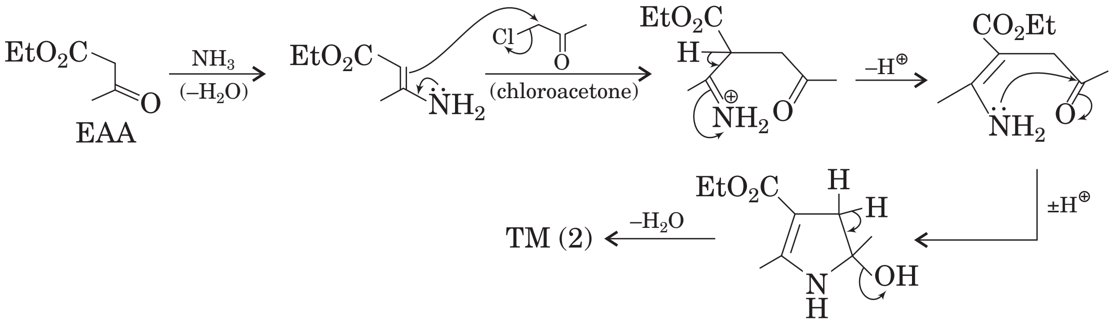
Retrosynthetic analysis

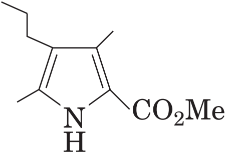


TM (2)

Hentzsch pyrrole synthesis involves condensation of an α-haloketone with a β-keto ester in the presence of ammonia (or a 1° amine).

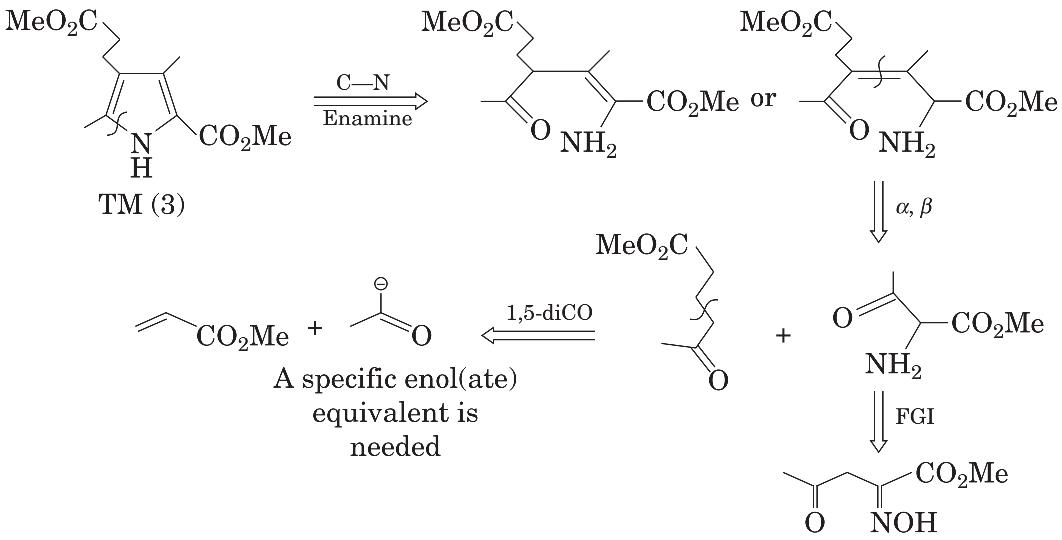
Synthesis



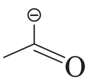
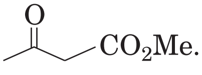
3. 

TM (3)

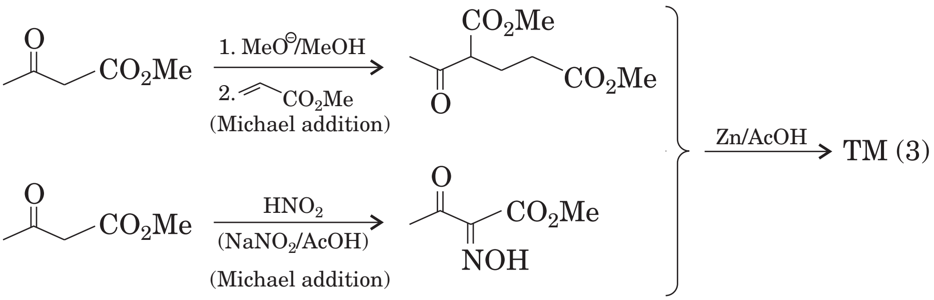
Retrosynthetic analysis



A specific enol(ate) equivalent is needed

The specific enolate equivalent of  is .

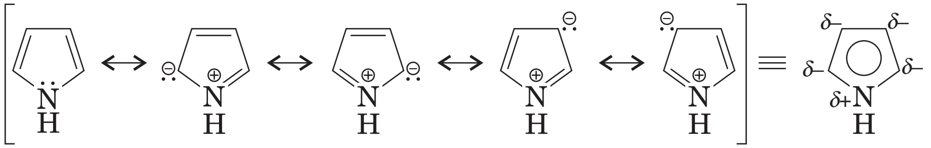
Synthesis



6.2.1.2 Properties and Reactions

Pyrrole is a liquid having boiling point 131°C. It rapidly darkens on exposure to air. A characteristic reaction is the turning red of a pine splint moistened with HCl when exposed to the vapour of pyrrole.

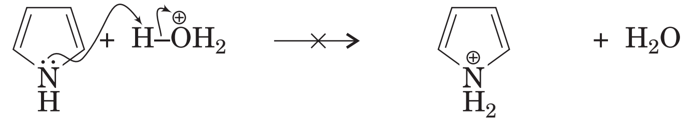
Because of the contribution of the lone pair of electrons of the nitrogen atom to the formation of an aromatic sextet [$(4n + 2)\pi$ electrons, where $n = 1$], the availability of the lone pair for protonation is very much decreased and because of this, pyrrole is a very weak base ($pK_a = 0.4$). In the presence of acid, pyrrole undergoes protonation on carbon instead of nitrogen. This may be explained as follows. Pyrrole is a resonance hybrid of the following contributing structures:



Resonance structures of pyrrole

Resonance hybrid

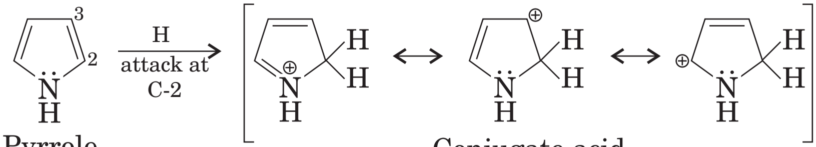
The resonance hybrid of pyrrole indicates that there is a partial positive charge on nitrogen and a partial negative charge on each carbon. Therefore, when pyrrole is acidified it is not protonated on nitrogen because protons tend to be expelled by nitrogen. Protonation actually occurs at the negatively polarized carbon. This may also be explained in terms of the stability of the conjugate acids involved in C- and N-protonation. Protonation of the pyrrole nitrogen would disrupt the aromatic system of six π-electrons by taking the nitrogen unshared pair out of the sextet. Also, the positive charge on nitrogen is localized.



Pyrrole

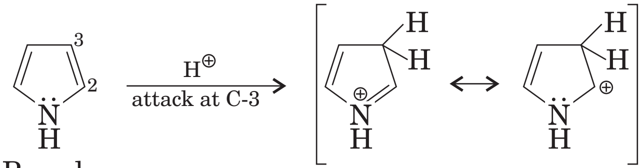
Conjugate acid
(less stable and not formed
because it is not aromatic and
the +ve charge is localized)

Although protonation of the ring carbon disrupts the aromatic π-electron system, the conjugate acid, i.e., the carbocation, is resonance-stabilized. Hence, the conjugate acid obtained on protonation on carbon is relatively more stable. Thus, protonation occurs on carbon rather than on nitrogen. Now, it occurs preferably at C-2 instead of C-3 because the corresponding conjugate acid in relatively more stable



Pyrrole

Conjugate acid
(somewhat more stable due to
greater number of resonance structures)



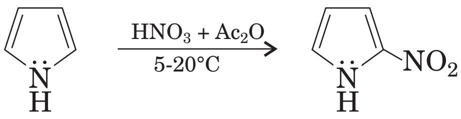
Pyrrole

Conjugate acid
(less stable due to lesser
number of resonance structures)

Pyrrole is very reactive towards the usual electrophilic reagents, and in fact, the most important chemical reactions of pyrrole are electrophilic substitutions.

1. Electrophilic substitutions It has already been discussed that electrophilic substitution in pyrrole takes place preferably at the 2-position because the transition state leading the formation of the intermediate carbocation for 2-attack is of lower energy than that for 3-attack. Some typical electrophilic substitution reactions of pyrrole are as follows:

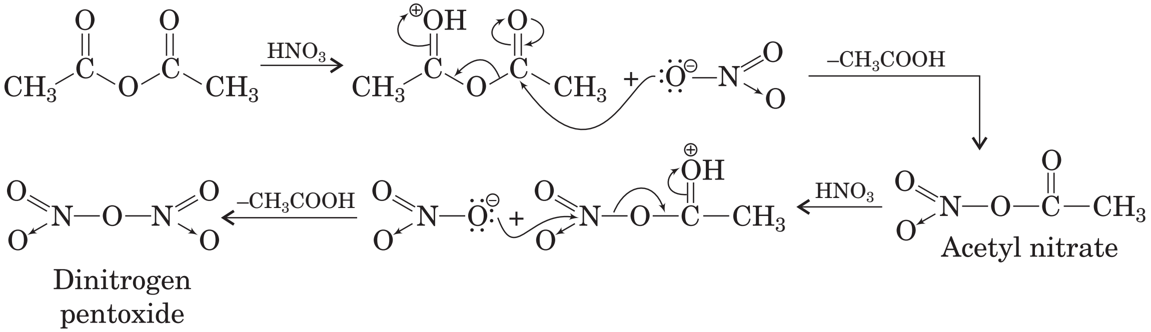
(i) Nitration Nitration of pyrrole cannot be carried out with mixed acid (conc. HNO_3 + conc. H_2SO_4) because this reagent causes extensive decomposition of the pyrrole ring resulting in the formation of tar. Pyrrole forms 2-nitropyrrole when nitrated with nitric acid in acetic anhydride.

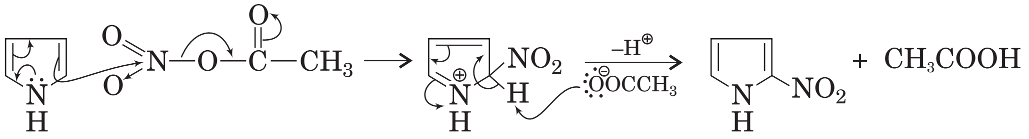


Pyrrole

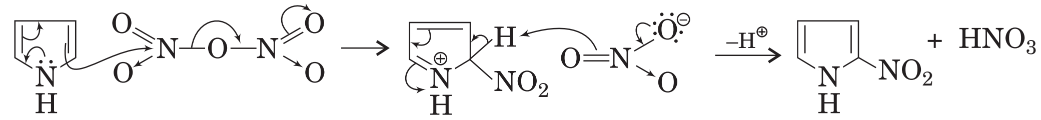
2-Nitropyrrole
(major)

Mechanism of the reaction The nitrating species involved in nitration with Ac_2O–HNO_3 is acetyl nitrate or dinitrogen pentoxide. These are generated as follows:

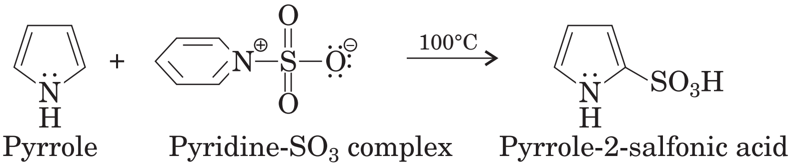




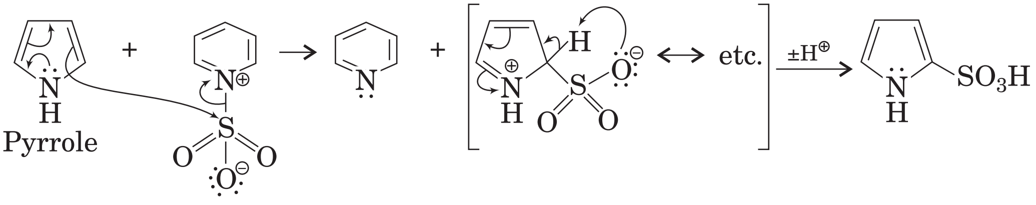
or,



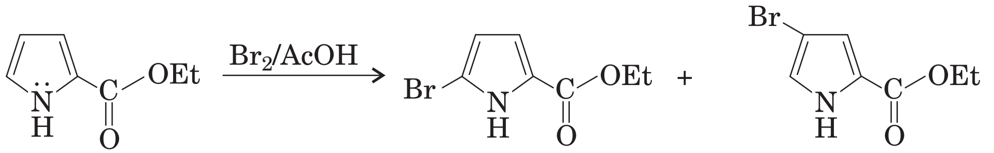
(ii) Sulphonation Pyrrole forms resinous material with sulphuric acid at ordinary temperature. However, sulphonation leading to the formation of pyrrole-2-sulfonic acid can be achieved in the presence of the mild sulfonating agent pyridine-SO$_3$ complex at 100°C.



Mechanism of the reaction:



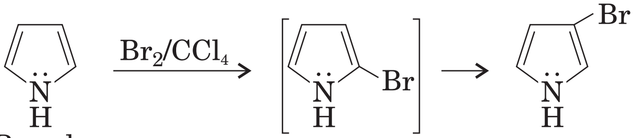
(iii) Halogenation Bromination of pyrrole with Br$_2$/AcOH gives 2,3,4,5-tetrabromopyrrole. However, pyrrole substituted with electron-attracting substituents gives monobromopyrrole (4 and 5-bromo derivative). Bromination in carbon tetrachloride, on the other hand, yields 3-bromopyrrole by isomerization of thermodynamically less stable 2-isomer.



Ethyl pyrrole-2-corboxylate

Ethyl 5-bromopyrrole-2-carboxylate

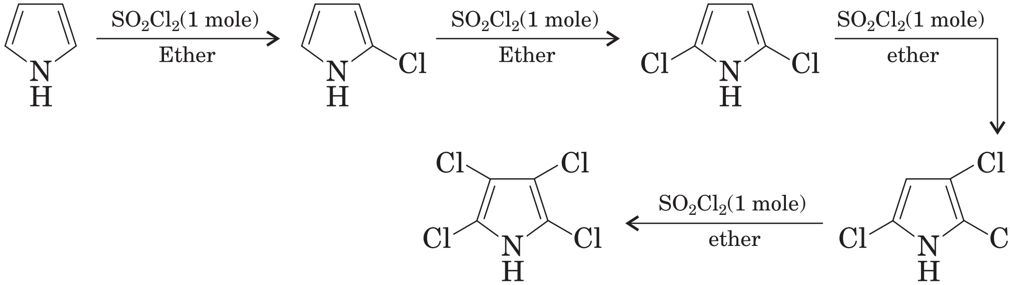
Ethyl 4-bromopyrrole-2-carboxylate



Pyrrole

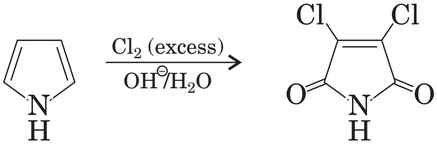
3-Bromopyrrole

Chlorination of pyrrole with sulphuryl chloride gives a mixture of mono-, di-, tri-, and tetrachloropyrroles depending on amount of SO_2Cl_2 used.



2,3,4,5-Tetrachloropyrrole

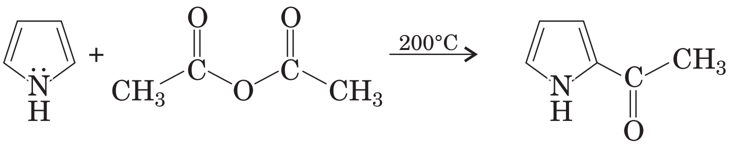
Chlorination of pyrrole with Cl_2 gas in warm aqueous alkali produces 3,4-dichloromaleimide.



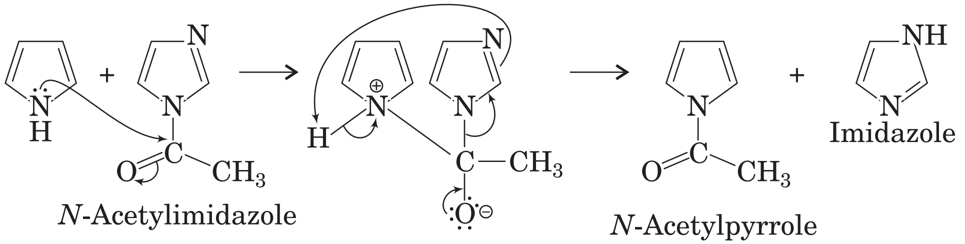
Pyrrole

3,4-Dichloromaleimide

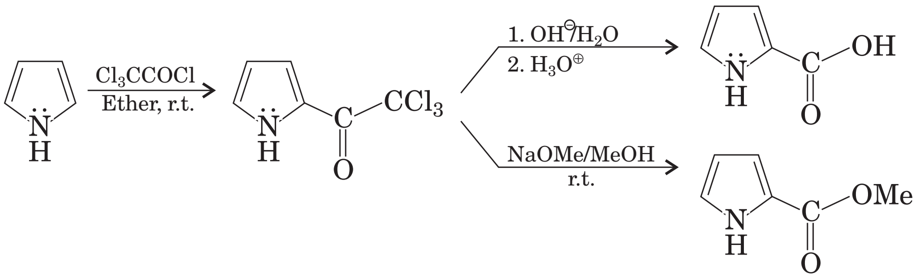
(iv) Acylation Direct acetylation of pyrrole with acetic anhydride at 200°C leads to 2-acetylpyrrole as the major product, but no *N*-acetylpyrrole. *N*-acetylpyrrole can be obtained in high yield by heating pyrrole with *N*-acetylimidazole.



2-Acetylpyrrole
(major)



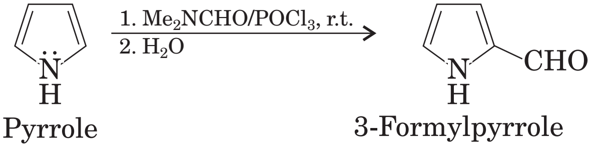
The more reactive trifluoroacetic anhydride or trichloroacetyl chloride react with pyrrole efficiently, even at room temperature, to yield 2-substituted products. Alcoholysis or hydrolysis of the resulting compounds provides a smooth route to pyrrole-2-esters or -acids.



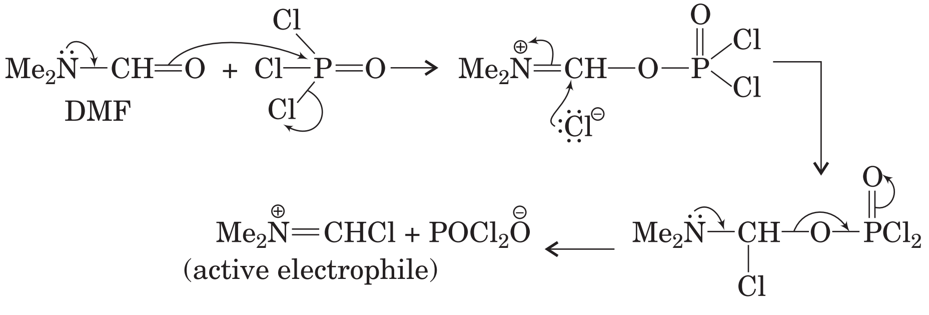
Strong electron-attracting (m-directing) substituent (e.g., —$COCl_3$) at a pyrrole α-position tend to override the intrinsic pyrrole regioselectivity and further substitution then takes place mainly C-4 and not at the remaining α-position.

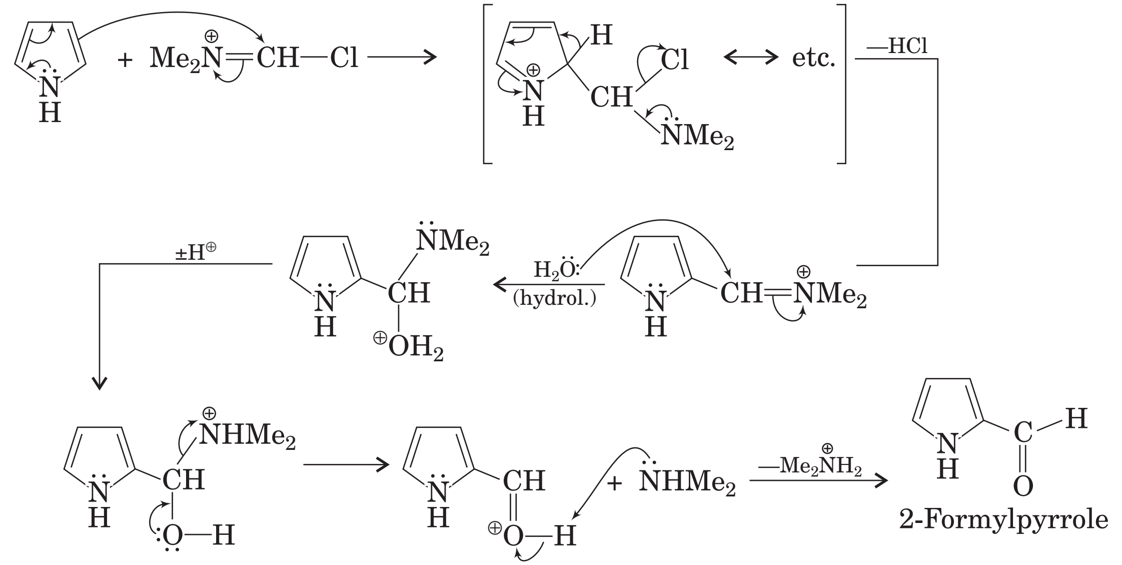
Friedel–Crafts alkylation of pyrrole can only be carried out when there is an electron-withdrawing group in the ring.

(v) Vilsmeier–Haak formylation 2-Formylation of pyrrole can be obtained by the Vilsmeier–Haak reaction in which pyrrole is treated with phosphorous oxychloride ($POCl_3$) and *N*, *N*-dimethylformamide (DMF) and then hydrolyzing the resulting iminium salt.

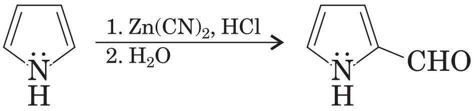


Mechanism of the reaction:





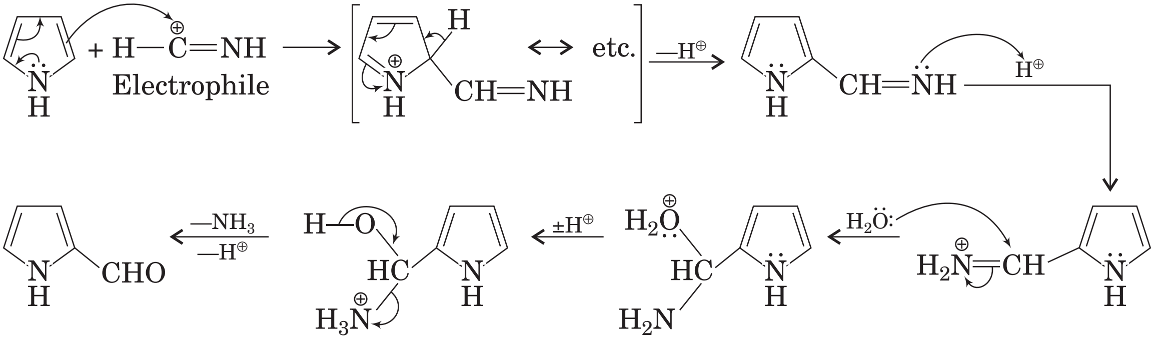
(vi) Gatterman reaction Pyrrole-2-carbaldehyde can be prepared by the Gatterman reaction in which pyrrole is treated with HCl and $Zn(CN)_2$ fallow by hydrolysis.



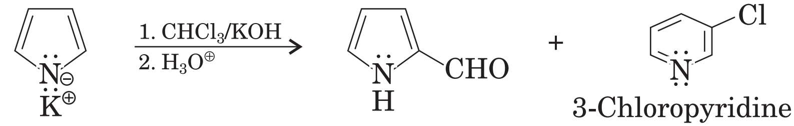
Mechanism of the reaction:

$$Zn(CN)_2 + 2HCl \rightleftharpoons ZnCl_2 + 2HCN;\ ZnCl_2 + 2HCl \rightleftharpoons 2H^{\oplus} + ZnCl_4^{2\ominus}$$

$$2H{-}C{\equiv}N + 2H^{\oplus}\ ZnCl_4^{2\ominus} \rightleftharpoons 2[H{-}C{\equiv}\overset{\oplus}{N}H \longleftrightarrow H{-}\overset{\oplus}{C}{\equiv}NH] + ZnCl_4^{2\ominus}$$



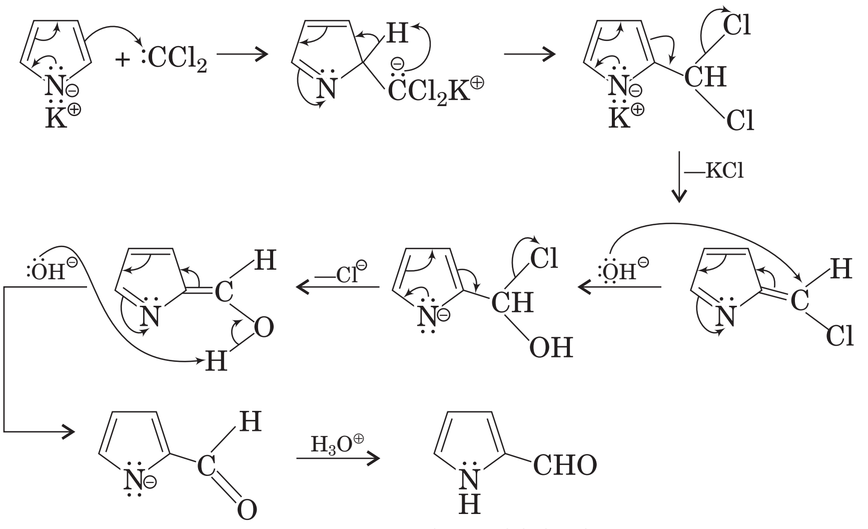
(vii) Reimer–Tiemann reaction Potassiopyrrole undergoes the Reimer–Tiemann reaction to give pyrrole-2-aldehyde when treated with chloroform and alkali. An abnormal product 3-chloropyridine is also obtained.



Potassiopyrrole Pyrrole-2-aldehyde 3-Chloropyridine

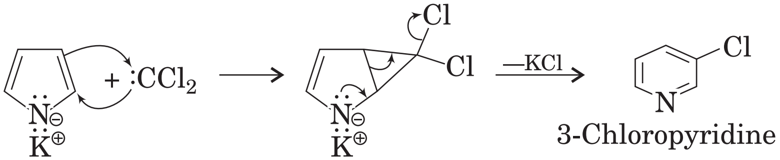
Mechanism of the reaction When pyrrole is fused with KOH, potassiopyrrole is obtained. This undergoes the Reimer-Tiemann reaction involving the electrophilic species dichlorocarbene (:CCl_2) as follows:

$$H\ddot{\underset{\cdot\cdot}{O}}^{\ominus} + H-CCl_3 \xrightleftharpoons{\text{fast}} H_2O + \overset{\ominus}{\ddot{C}}Cl_2-Cl \xrightarrow{\text{slow}} :CCl_2 + Cl^{\ominus}$$



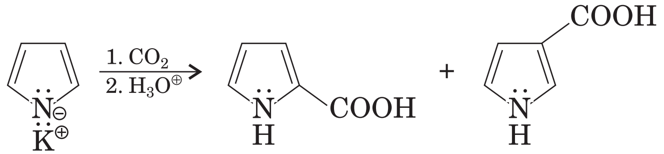
Pyrrole-2-aldehyde

3-Chloropyrine is obtained by a ring expansion process:

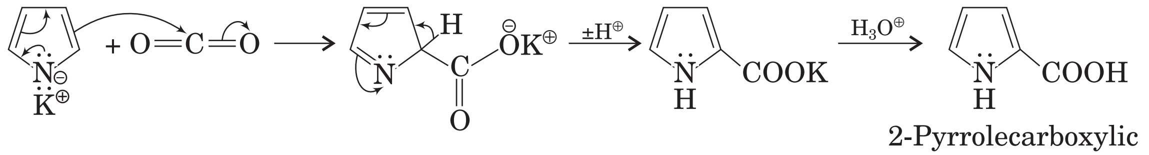


3-Chloropyridine

(viii) Kolbe–Schmitt reaction Potassiopyrrole reacts with carbon dioxide to form, after acidification, 2- and 3-pyrrolecarboxylic acid.

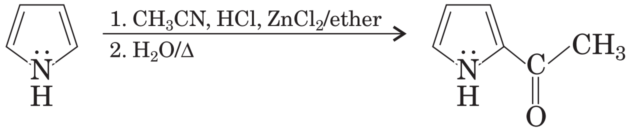


Mechanism of the reaction:

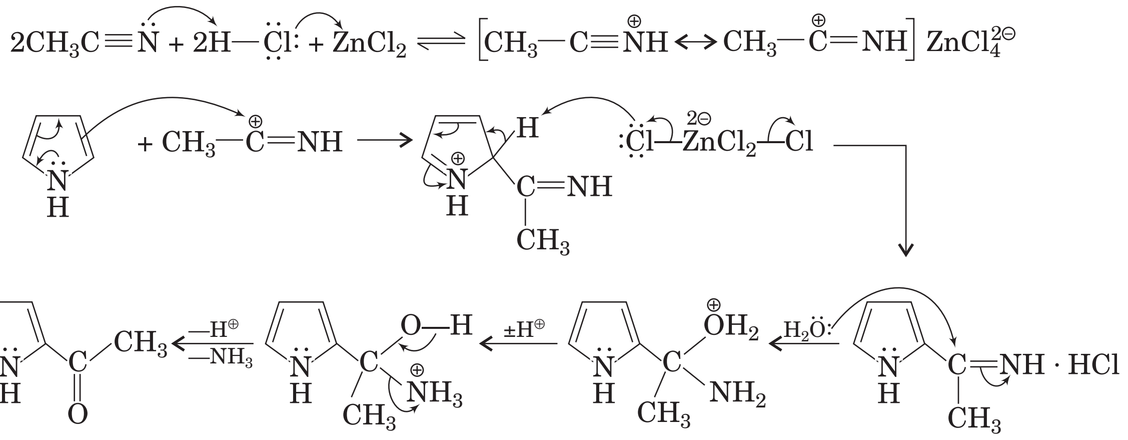


2-Pyrrolecarboxylic acid (major)

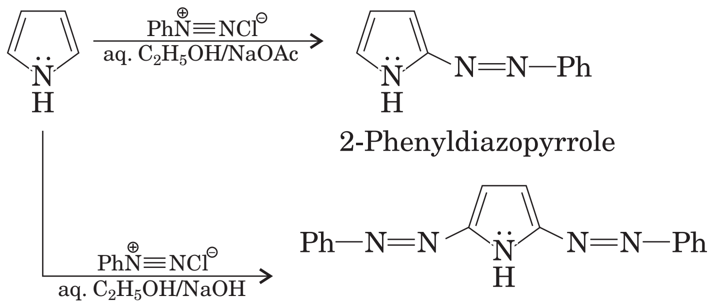
(ix) Houben–Hoesch reaction 2-Acylpyrrole can be obtained by the Houben–Hoesch reaction, which consists in treatment of pyrrole with an aliphatic nitrile and HCl in the presence of the Lewis acid catalyst $ZnCl_2$.



Mechanism of the reaction:



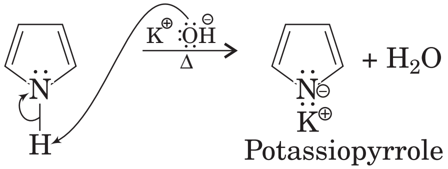
(x) Diazocoupling reaction Pyrrole undergoes diazocoupling with benzenediazonium chloride very easily to give 2- or 2,5-disubstituted products depending on the reaction conditions.



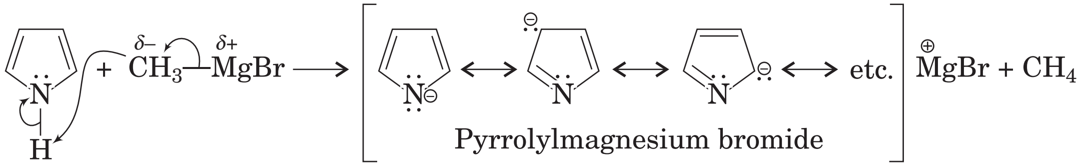
2-Phenyldiazopyrrole

2,5-Diphenyldiazopyrrole

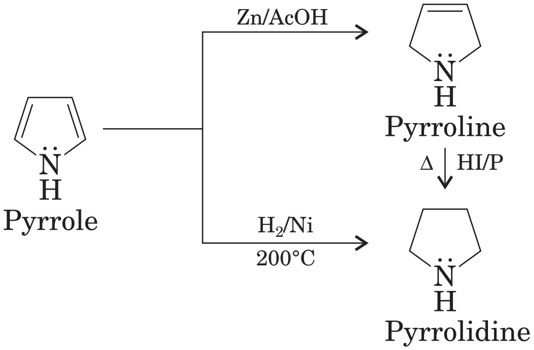
2. Acidic character Pyrrole is weakly acidic. When it is fused with solid KOH, the imino hydrogen is replaced by potassium, showing the acidic character of the compound.



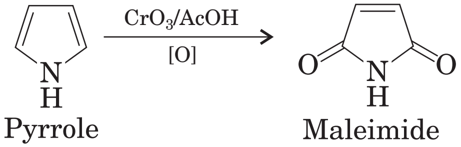
When pyrrole is treated with methylmagnesium bromide (a Grignard reagent), pyrrolylmagnesium bromide is obtained with the evolution of methane. This reaction also proves its acidic character.



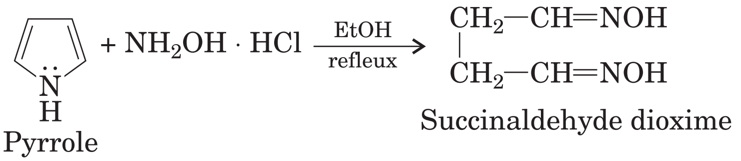
3. Reduction Pyrrole can be reduced to pyrroline by treating with zinc and acetic acid. Pyrroline can further be reduced to pyrrolidine (tetrahydropyrrole) on heating with HI and red phosphorus. Pyrrolidine can also be obtained directly by catalytic hydrogenation of pyrrole.



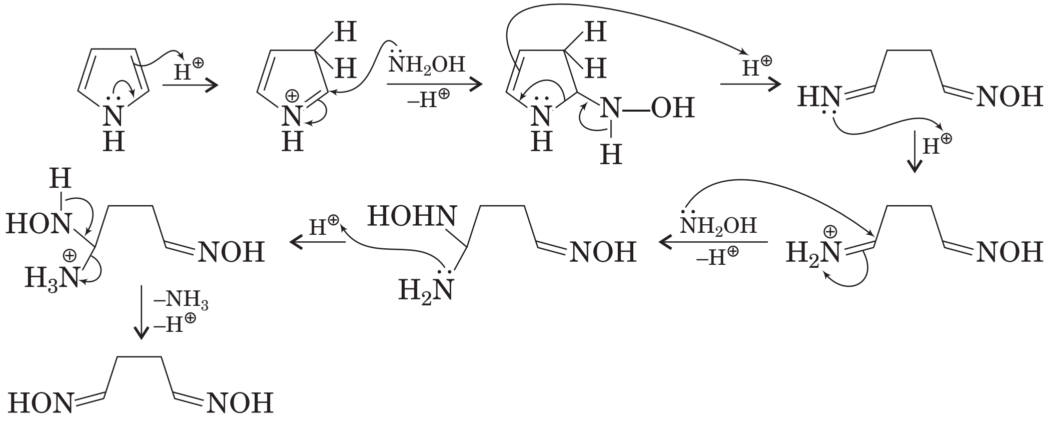
4. Oxidation Pyrrole can be oxidized by chromium trioxide in acetic acid to maleimide.



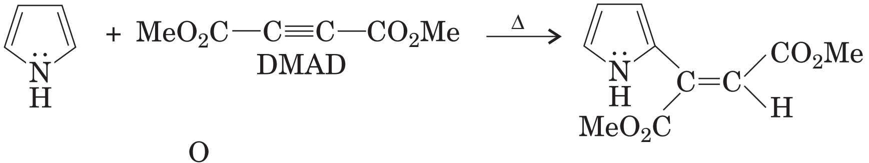
5. Ring Cleavage Reaction Pyrrole ring is not cleaved readily by acids or bases. However, when pyrrole is refluxed with an ethanolic solution of hydroxylamine hydrochloride ($NH_2OH \cdot HCl$), it undergoes ring cleavage resulting in the formation of succinaldehyde dioxime.

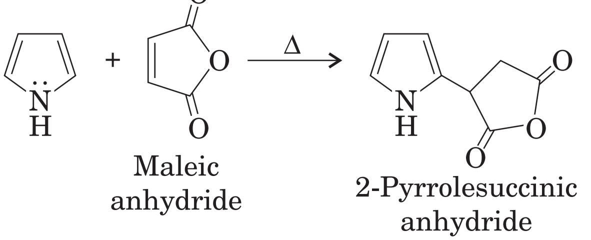


Mechanism of the reaction Pyrrole first undergoes protonation at C-3 to form 3*H*-pyrrolium cation which subsequently reacts with hydroxylamine.

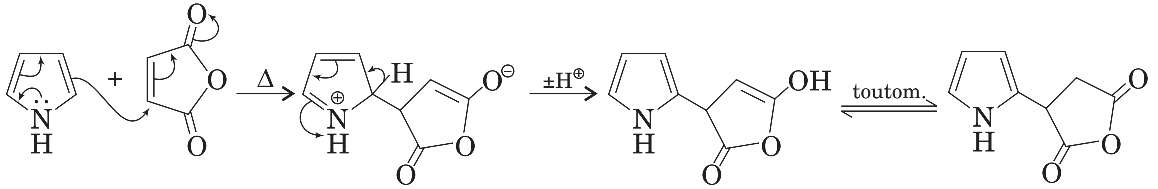


6. Diels–Alder reaction There is always an energy cost to be paid when the aromaticity of an aromatic heterocycle is lost in a Diels–Alder reaction leading to a nonaromatic product. Because of its aromatic character, pyrrole is less likely to function in reactions typical of a diene. In fact, unlike furan it does not undergo the Diels–Alder reaction. Depending on the nature of pyrrole and the experimental conditions employed, it appears to follow two different pathways: (i) a (4 + 2) cycloaddition or (ii) a Michael type of addition at the α-position. For example, when pyrrole is allowed to react with DMAD or maleic anhydride, it undergoes Michael type addition.

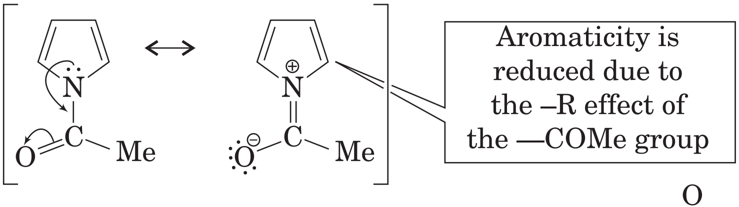


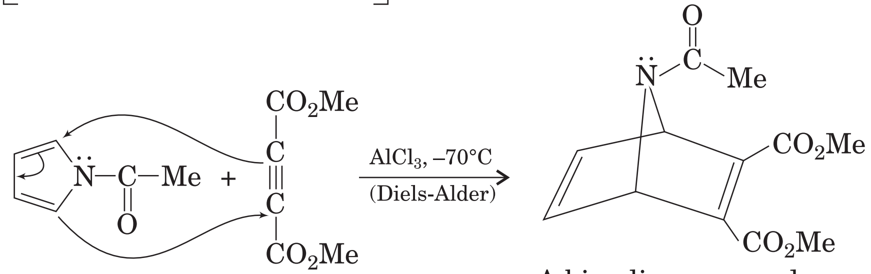


Mechanism



The presence of electron-attracting groups like —$COCH_3$, —SO_2Ph, etc. On the N atom reduces the aromaticity of pyrrole. Because of this, the diene property of that derivative of pyrrole becomes relatively strong and it forms a normal adduct in the presence of aluminium chloride (a Lewis acid).


Aromaticity is reduced due to the –R effect of the —COMe group



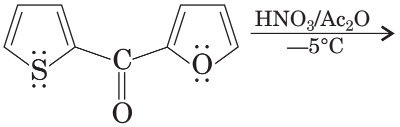
N-Acetylprrole (diene)

DMAD (dienophile)

A bicyclic compound (adduct)

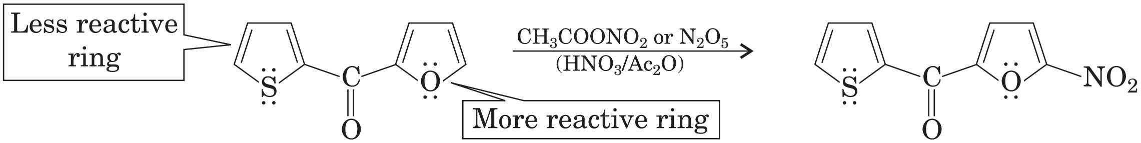
SOLVED PROBLEMS

1. **Give the structure of the mononitration product of the following compound and explain why it is formed:**



Give the mechanism of the reaction involved. **[C.U. 2011]**

Solution Since furan is relatively more reactive than thiophene towards electrophilic substitution reaction, the furan ring of 2-furyl 2′-thienyl ketone undergoes nitration at a faster rate to give 5-nitro-2-furyl 2′-thienyl ketone nearly exclusively.



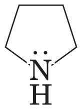
2-Furyl 2′-thienyl ketone 5-Nitro-2-furyl 2′-thienyl ketone

[For the mechanism of the reaction, see **article no. 6.2.2.2.**]

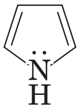
2. Explain why pyrrole exhibits close similarity with aniline.

Solution In pyrrole molecule, the nonbonding electrons on nitrogen is involved in constituting an aromatic sextet [$(4n + 2)\pi$ electrons, where $n = 1$]. As a consequence, the ring becomes rich in electron (π-excessive: six electrons in five orbitals) and because of this, it behaves like a reactive, i.e., activated benzene derivative like aniline (in which the ring becomes electron rich by the +R effect of the —NH_2 group), undergoing ready electrophilic attack.

3. (a) The dipole moments of pyrrole and pyrrolidine are similar in magnitude but have opposite directions. Indicate the direction of dipole moment in each compound and explain.



$\mu = 1.57$ D

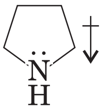


$\mu = 1.80$ D

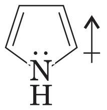
(b) Should the dipole moment of 3,4-dichloropyrrole be greater or less than that of pyrrole? Give your reasoning.

Solution

(a) In pyrrole, the dipole moment points towards the ring away from the nitrogen atom, whereas in its saturated analogue pyrrolidine, it points towards the nitrogen atom.



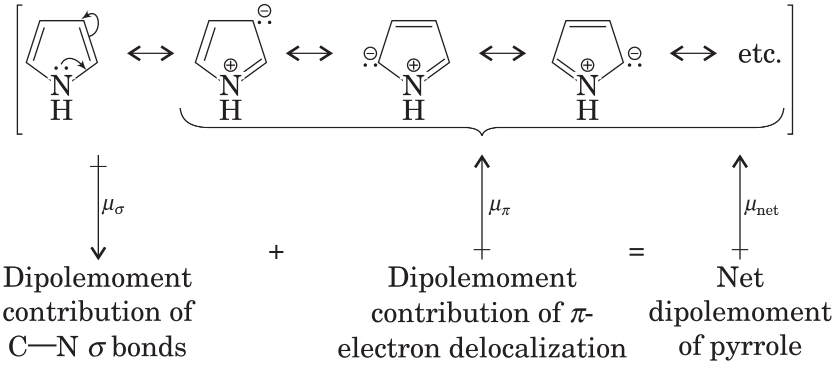
Pyrrolidine
($\mu = 1.57$ D)



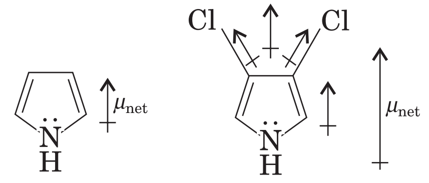
Pyrrole
($\mu = 1.80$ D)

The dipole moment of pyrrolidine is attributed to the bond dipoles of its polar C—N single bonds. That is, electrons of the σ bonds are pulled towards the nitrogen because of its electronegativity and the dipole points towards the nitrogen atom. The same effect is present is pyrrole, but in addition there is a second effect: the resonance delocalization of nitrogen unshared pair of electrons into the ring. This tends to push electrons away from nitrogen into the π-electron system of the ring.

Since the π-moment is larger than the σ-moment, the net moment points towards the ring away from the N atom.


N
H
etc.
μ_σ
μ_π
μ_{net}
+
=
Dipolemoment contribution of C—N σ bonds
Dipolemoment contribution of π-electron delocalization
Net dipolemoment of pyrrole

(b) Since the resulting moment of the two C—Cl bonds will lie in the same direction as that of the net moment of pyrrole, they will be added and hence, the dipole moment of 3,4-dichloropyrrole will be greater than pyrrole.



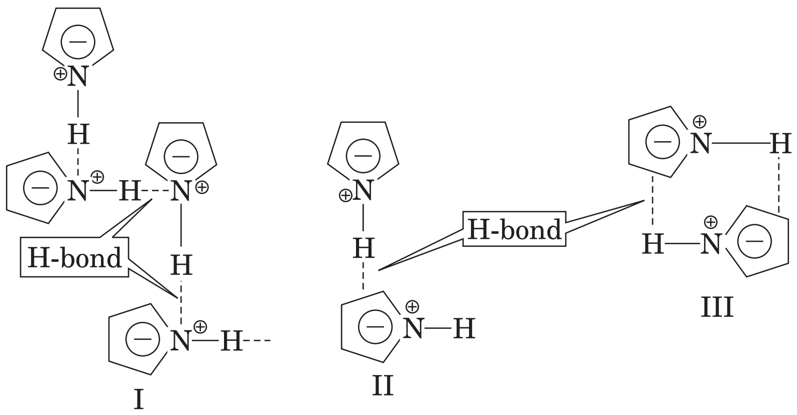
μ = 1.80 D μ = >1.80 D

4. **Account for the following observations:**
   - **(a) Pyridine is miscible in water, whereas pyrrole is only slightly soluble in water.**
   - **(b) The boiling point of pyrrole is higher than that of furan.**
   - **(c) Cyclopentadiene is a much stronger acid than pyrrole.**
   - **(d) Pyrrole is a weaker base than imidazole.**
   - **(e) Pyridine is a stronger base than pyrrole.**
   - **(f) *N*-methylpyrrole does not undergo the Diels–Alder reaction with maleic anhydride. [C.U. 2010]**

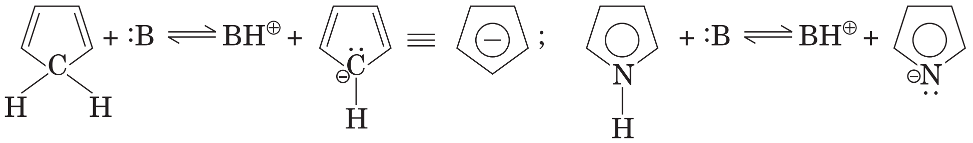
Solution

(a) The undisturbed electron density on the nitrogen atom in pyridine allows for H-bonding with water molecules and so, pyridine is miscible. On the other hand, the lack of electron-density on nitrogen (for maintaining aromatic sextet) precludes H-bonding and therefore, pyrrole is only slightly soluble in water.

(b) Pyrrole has a higher boiling point than furan because pyrrole molecules remain associated through intermolecular H-bonding. Since there is no hydrogen attached to oxygen, association through intermolecular H-bonding is not possible in the case of furan. The three suggested models (I–III) are as follows:

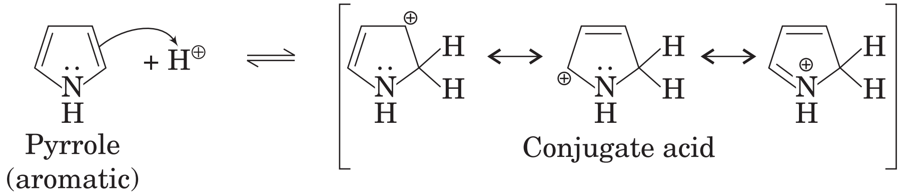


(c) In the conjugate base of pyrrole, the negative charge remains predominantly on the more electronegative nitrogen atom, whereas in the conjugate base of cyclopentadiene, the negative charge remains on the less electronegative carbon atom. Since a more electronegative atom accommodates a negative charge better than a less electronegative atoms, the conjugate base of pyrrole in expected to be more stable and so, pyrrole is expected to be more acidic than cyclopentadiene. However, the reverse is true. The conjugate base of cyclopentadiene is an aromatic system, whereas cyclopentadiene is not. Therefore, it is energetically profitable for cyclopentadiene to release a proton. On the other hand, both pyrrole and its conjugate base are aromatic. Therefore, loss of a proton is not energetically profitable in this case. This explains why cyclopentadiene is a much stronger acid than pyrrole.



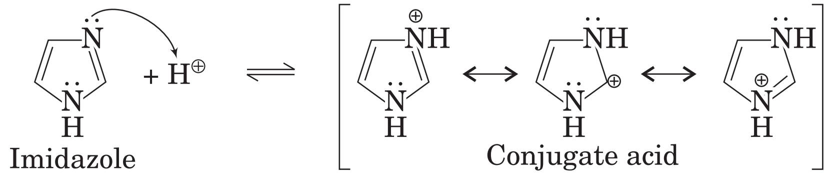
Cyclopentadiene (nonaromatic) Conjugate base (aromatic) Pyrrole (aromatic) Conjugate base (aromatic)

(d) The conjugate acid of pyrrole is not much stabilized by resonance (only in one structure octet of every atom is filled up) and protonation causes loss of aromaticity of pyrrole. Imidazole undergoes protonation on the doubly bonded nitrogen atom (the nonbonding electrons on it is not part of the aromatic sextet) and the resulting conjugate acid is much stabilized by resonance (two of the resonance structures are equivalent and octet of every atom in them is filled up). Also, on protonation, aromaticity of imidazole is not lost. For this reason, the protonation equilibrium is relatively more favourable for imidazole compared to pyrrole. Hence, pyrrole is a weaker base than imidazole.



Pyrrole (aromatic)

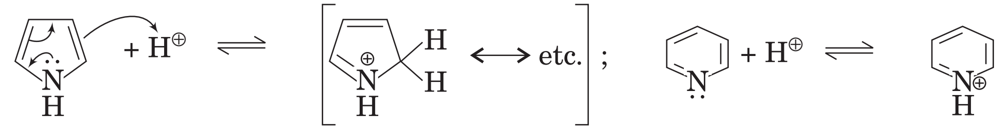
Conjugate acid



Imidazole (aromatic)

Conjugate acid

(e) The marked contrast between the basicities of pyrrole and pyridine can be well understood by considering the role of nitrogen's unshared electron pair in the aromaticity of each heterocycle. The nonbonding electrons on the N atom of pyrrole is involved in the aromatic sextet and are, therefore, less available for coordinating with a proton. On the other hand, the nonbonding electrons on the N atom of pyridine are not part of the aromatic sextet and are, therefore, more available for coordinating with a proton. Again, on protonation, the aromaticity of pyrrole is destroyed, whereas the aromaticity of pyridine remains intact. For this reason, pyridine is a stronger base than pyrrole.

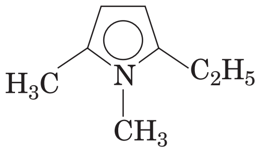


Pyrrole (aromatic) | Conjugate acid (nonaromatic) | Pyridine (aromatic) | Conjugate acid (aromatic)

(f) See **article no. 6.2.1.2** (Diels–Alder reaction).

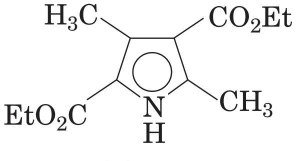
5. Predict the starting materials for the synthesis of each of the following compounds:

(a)



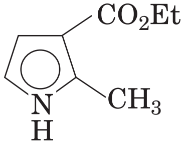
(by *Paal-Knorr synthesis*)

(b)



(by *Knorr pyrrole synthesis*)

(c)

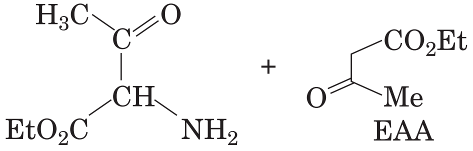


(by *Hantzsch pyrrole synthesis*)

Solution

(a) $CH_3COCH_2CH_2COC_2H_5$ + CH_3NH_2
Heptane-2,5-dione Methylamine

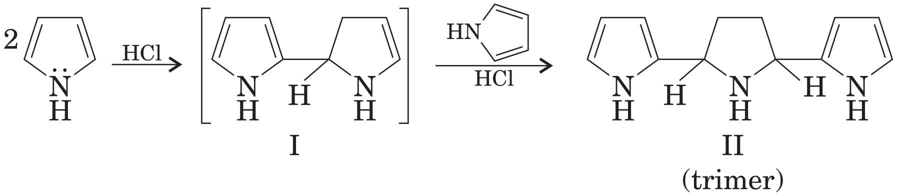
(b)



Ethyl 2-amino-3-oxobutanoate

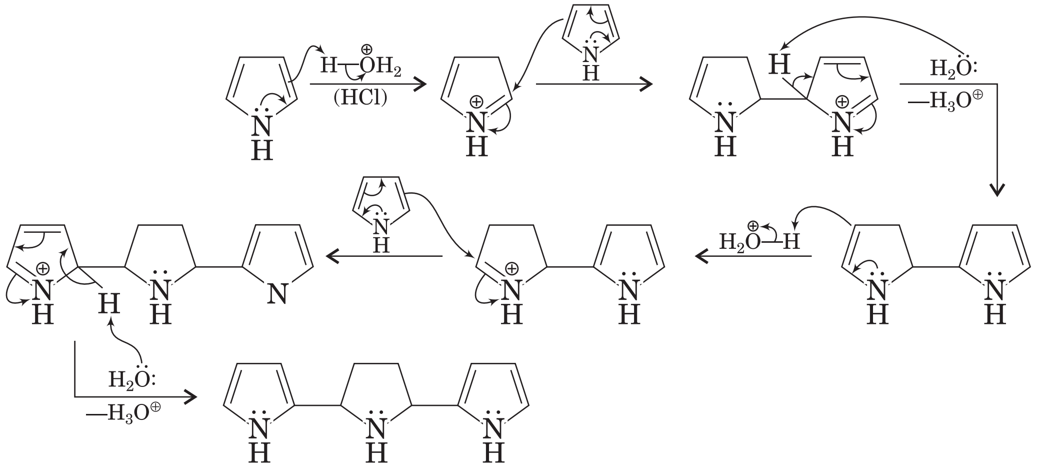
(c) $CH_3COCH_2CO_2Et + ClCH_2CHO + NH_3$
EAA

6. Pyrrole produces the crystalline compound II through the formation of the intermediate I when treated with 5.5 (N) HCl at 0°C for 30 s.



Suggest a mechanism for each step of this reaction sequence.

Solution The mechanism for the formation of the dimer I and the trimer II involves the steps as follows:



7. Identify the compounds I–V in the following two reaction sequences:

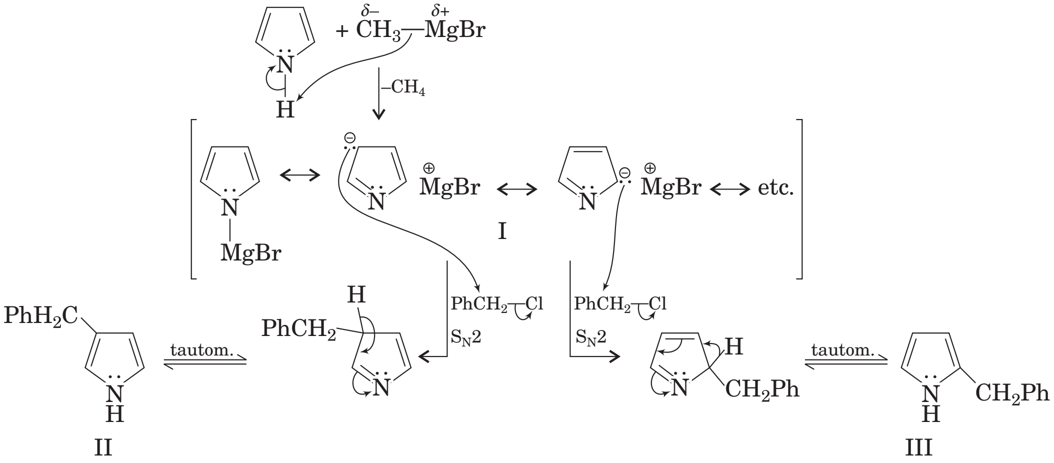
(a) Pyrrole + $CH_3MgBr \longrightarrow I \xrightarrow{PhCH_2Cl}$ II + III (isomers)

(b) Pyrrole + Potassium $\longrightarrow IV \xrightarrow{PhCH_2Cl} V$

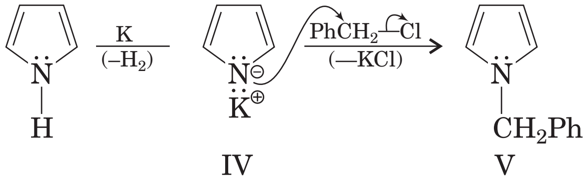
Explain the difference in the nature of the final products obtained in the two reaction sequences.

Solution

(a)



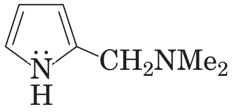
(b)



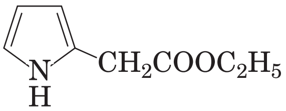
Since potassium is more electropositive than magnesium, the negative charge is concentrated more on nitrogen than on carbon in potassiopyrrole compared to the Grignard reagent in which $\rangle N^{\ominus}$ binds with $\overset{\oplus}{\mathrm{MgBr}}$ and becomes a less reactive site. So, in the reaction sequence (a), *C*-alkylation occurs (at C-3 and C-2) to give II and III, while in the reaction sequence (b), *N*-alkylation occurs to give V.

8. **Suggest a mechanism for each of the following reactions:**

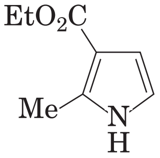
(a) Pyrrole $\xrightarrow[HCl/CH_3OH/\Delta]{HCHO/Me_2NH}$



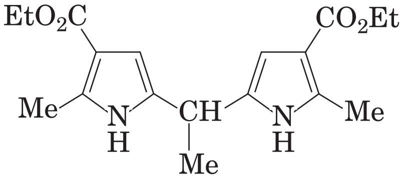
(b) Pyrrole + $N\equiv\overset{\oplus}{N}-\overset{\ominus}{C}HCOOC_2H_5 \xrightarrow[100°C]{Cu}$ **[C.U. 2013]**



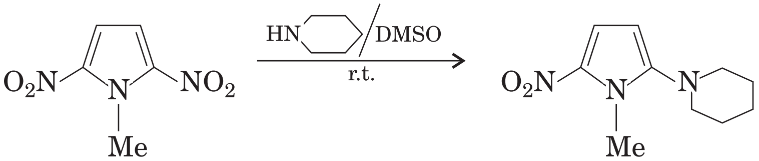
(c)



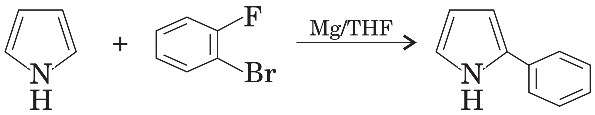
$\xrightarrow[EtOH,\ 100°C]{CH_3CHO,\ HCl}$



(d)



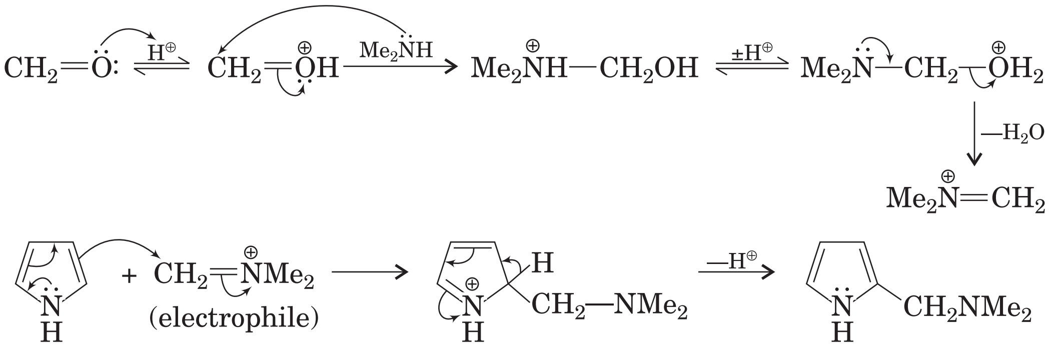
(e)



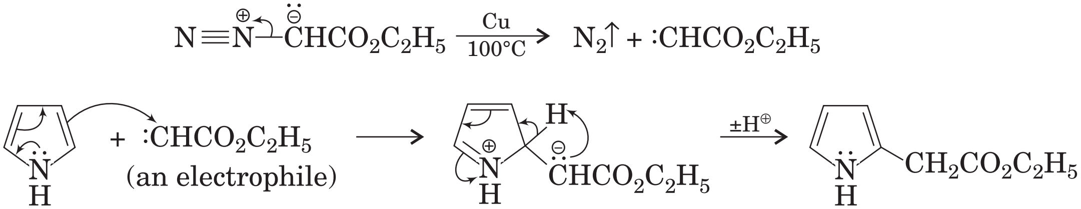
[C.U. 2015]

Solution

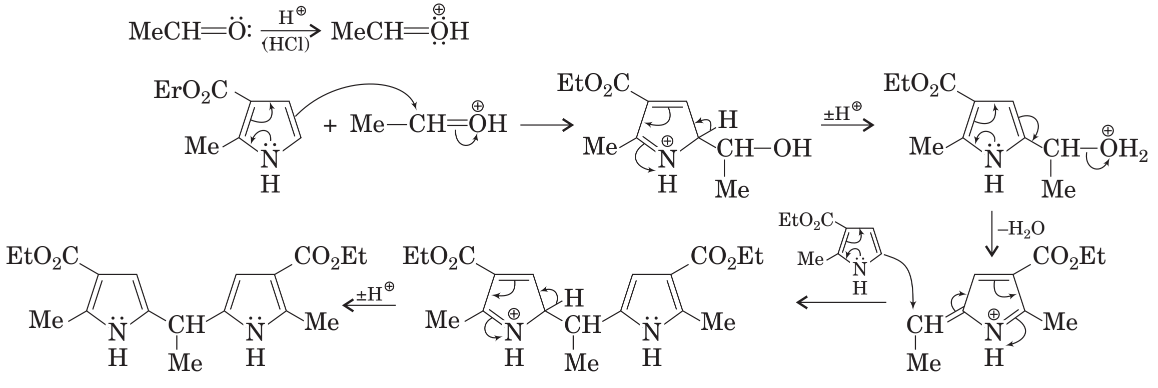
(a) The *Mannich reaction* of pyrrole involving formation of a methyleneammonium ion as the electrophile takes place as follows:



(b) This is a case of electrophilic substitution reaction in which carbethoxymethylene (:$CHCO_2Et$) obtained on copper-catalyzed decomposition of diazoacetic ester acts as the electrophile and an α-substituted pyrrolacetic ester is obtained as the product.

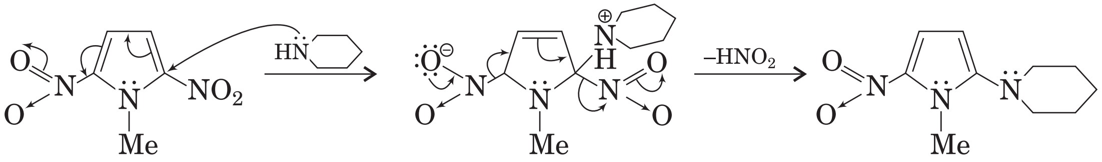


(c) Protonated acetaldehyde acts as an electrophile and substitution occurs at the free α-position. The intermediate alcohol undergoes protonation followed by loss of a molecule of water to form a resonance-stabilized carbocation. A second molecule of pyrrole reacts with this carbocation to yield a dipyrroethane.

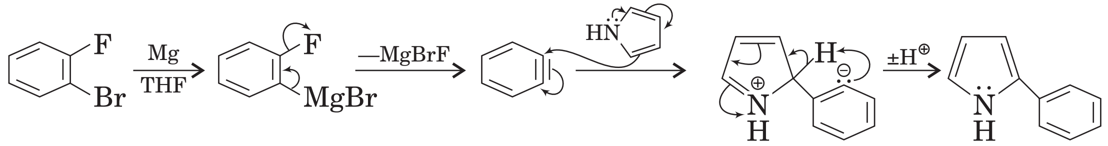


A dipyrroethane

(d) Due to presence of two electron-withdrawing —NO_2 groups, the pyrrole ring is considerably deactivated and undergoes nucleophilic substitution reaction in which one —NO_2 group is displaced by piperidine.

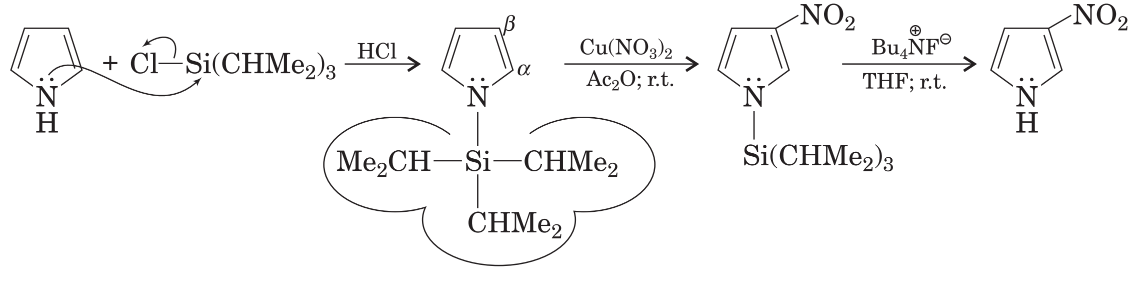


(e) The reaction proceeds through the formation of benzyne which reacts with pyrrole to give 2-phenylpyrrole.

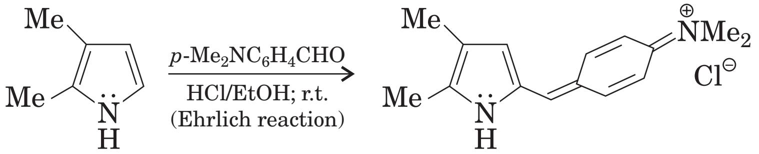


9. Nitration of pyrrole with a mixture of fuming HNO_3 and Ac_2O yields 2- and 3-nitropyrrole in 4:1 ratio. How would you prepare 3-nitropyrrole exclusively?

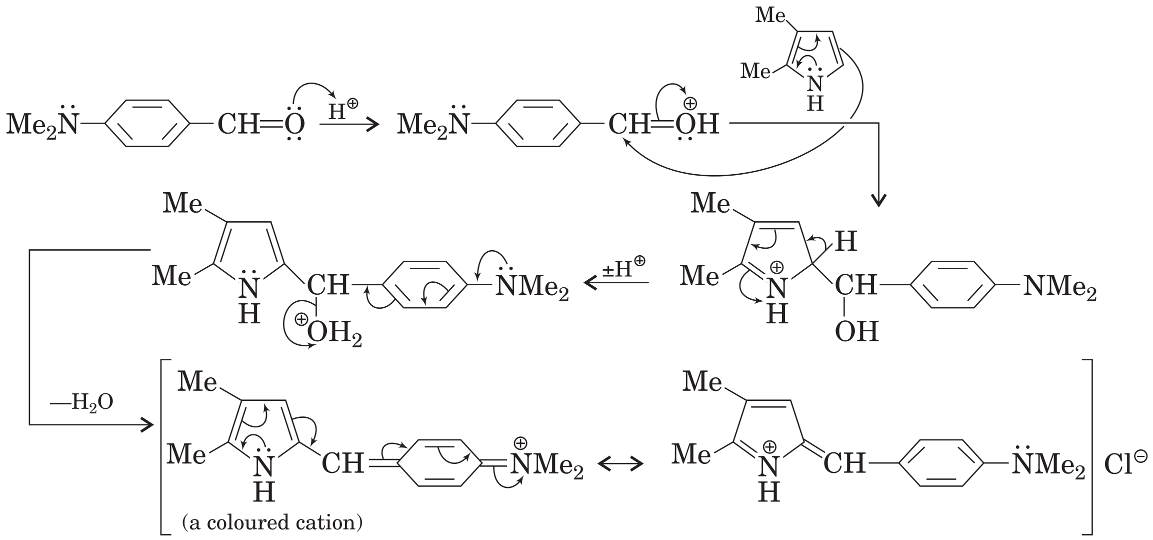
Solution *N*-substitution of pyrroles gives rise to increased proportions of β- or 2-substitution. If the group attached to nitrogen is very much bulky, α-substitution does not take place due to steric interaction and as a consequence, β-substitution takes place exclusively. α-Reactivity, for example, can be completely blocked with a very large substituent such as a triisopropylsilyl (TIPS) group. It is especially useful because it can be easily removed by treating with $Bu_4\overset{\oplus}{N}F^{\ominus}$. 3-Nitropyrrole can, therefore, be prepared as follows:



10. Condensations with aromatic aldehydes containing an appropriate electron-releasing group produce cations which are effectively stabilized by resonance to be isolated as a salt. The reaction with *p*-dimethylaminobenzaldehyde is the basis for the classical Ehrlich test in which deep red/violet colours are produced by pyrroles which have a free nuclear position. Suggest a reasonable mechanism for the following reaction:

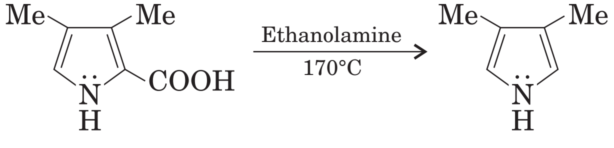


Solution The mechanism of this condensation involves the steps as follows:

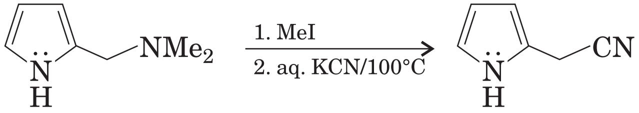


11. Write a curved-arrow mechanism for each of the following reactions:

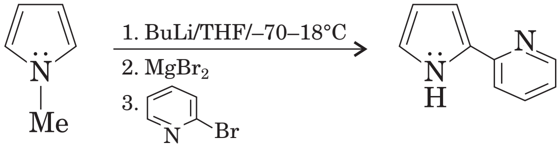
(a)



(b)

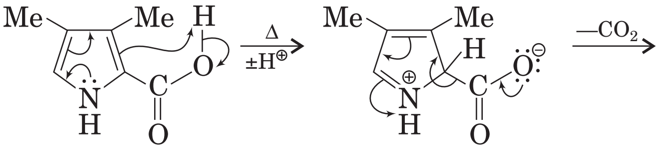


(c)

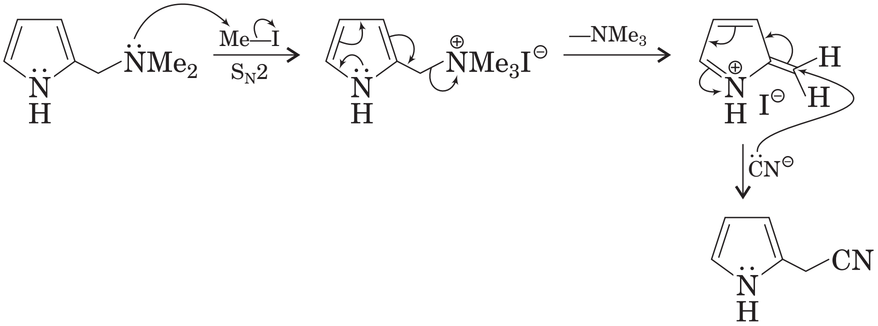


Solution

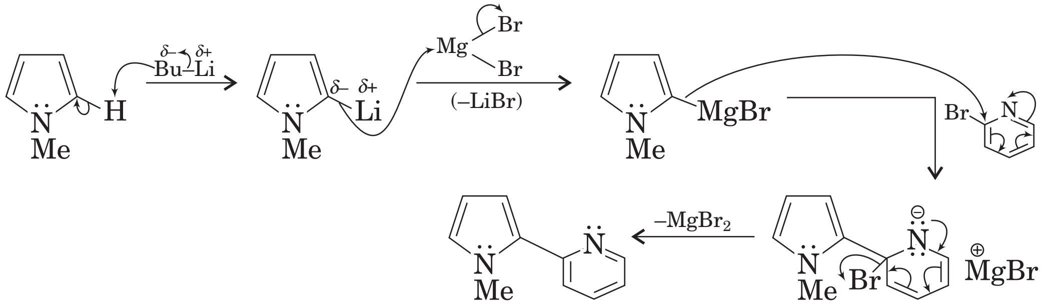
(a) When pyrrole acids are simply heated, loss of CO_2 occurs. The reaction is essentially an *ipso* displacement of carbon dioxide by proton.



(b) The substrate reacts with MeI to form a quaternary ammonium salt which loses a molecule of trimethylamine. The resulting compound undergoes nucleophilic attack by $CN^{\ominus}$ to give the product (an elimination/addition sequence).

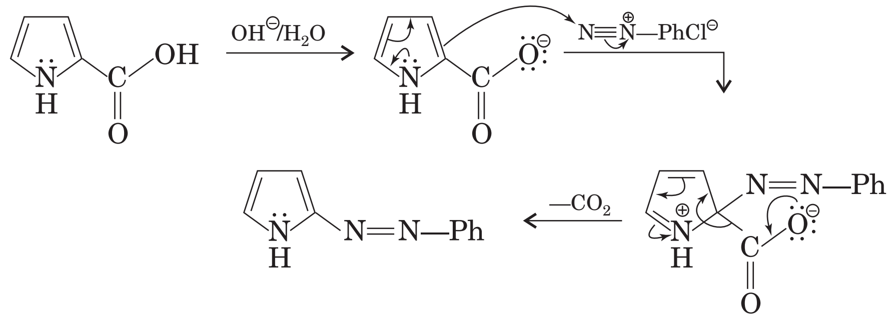


(c) Lithiation of the *N*-substituted pyrrole at C-2 followed by treatment with $MgBr_2$ leads to the formation of a Grignard reagent. This reacts with 2-bromopyridine (a nucleophilic aromatic displacement) to give the product.

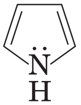


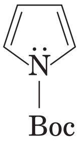
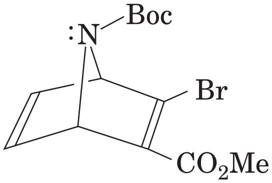
12. What happens when pyrrole-2-carboxylic acid in alkaline medium is treated with benzenediazonium chloride?

Solution When an alkaline solution of pyrrole-2-carboxylic acid is allowed to react with benzenediazonium chloride, a coupling reaction takes place at C-2 position along with decarboxylation.

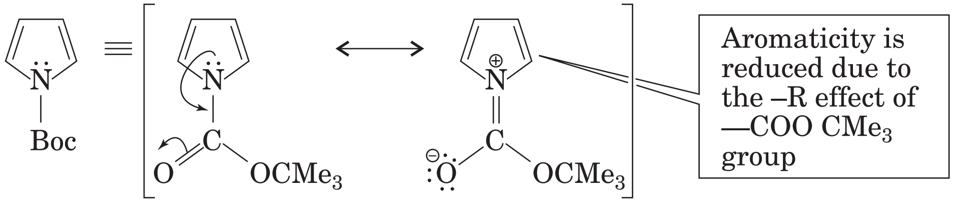


13. Explain the following observations:

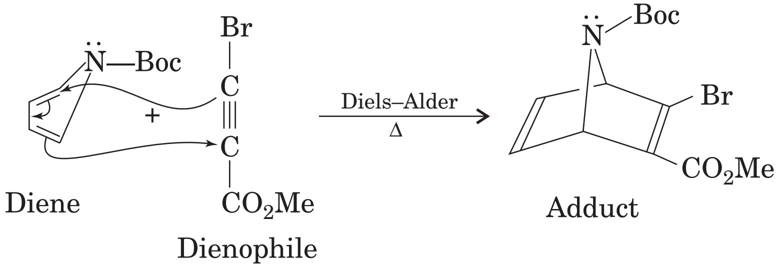
(a)  $+\ BrC{\equiv}CCO_2Me \xrightarrow{\Delta}$ No Diels–Alder reaction

(b)  $+\ BrC{\equiv}CCO_2Me \xrightarrow[\text{(Diels–Alder)}]{90^\circ\ C}$ 

Solution Because of considerable aromatic character, pyrrole does not undergo the Diels-Alder reaction. However, when an electron-attracting group remains attached to the nitrogen atom, the aromatic property of pyrrole is reduced. As a consequence, its diene property becomes strong and it undergoes the Diels–Alder reaction with an efficient dienophile. The *t*-butoxycarbonyl group or Boc group withdraws electron from nitrogen and so, *N*-*t*-butoxycarbonyl derivative of pyrrole undergoes the Diels–Alder reaction with BrC≡CCOMe to give the corresponding adduct.

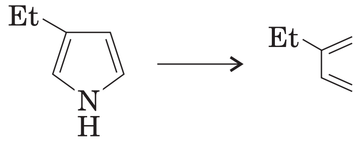


Aromaticity is reduced due to the –R effect of —COO CMe$_3$ group

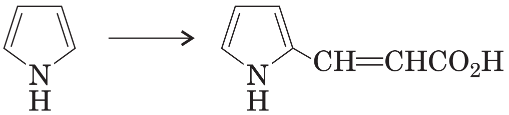


14. How would you carry out the following conversions:

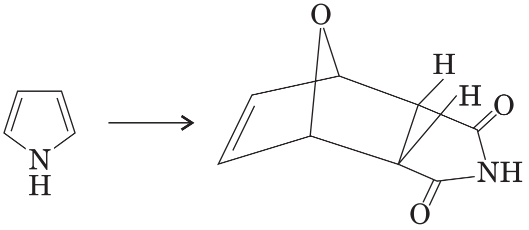
(a)



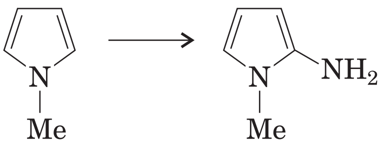
(b)



(c)

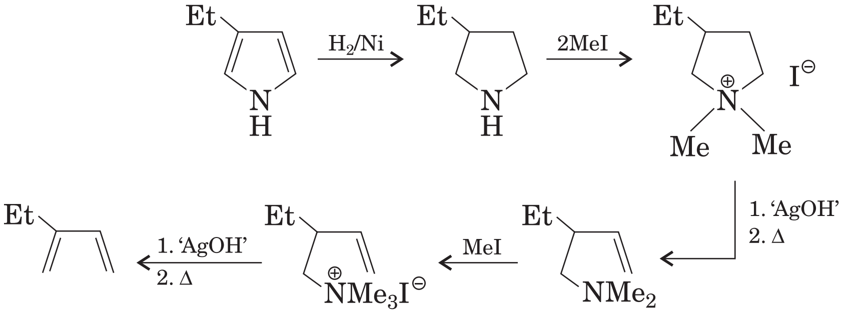


(d)



Solution

(a)



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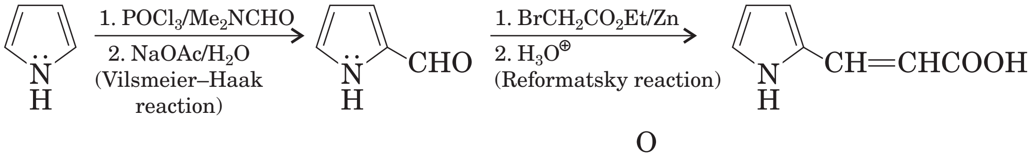

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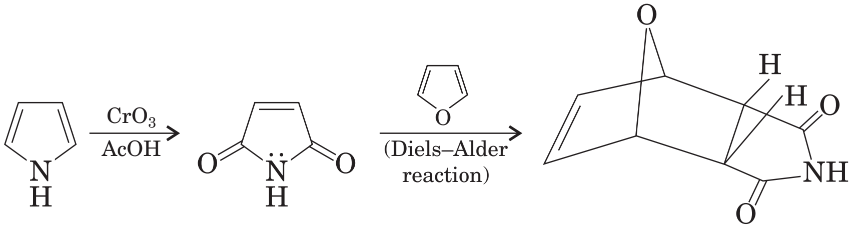
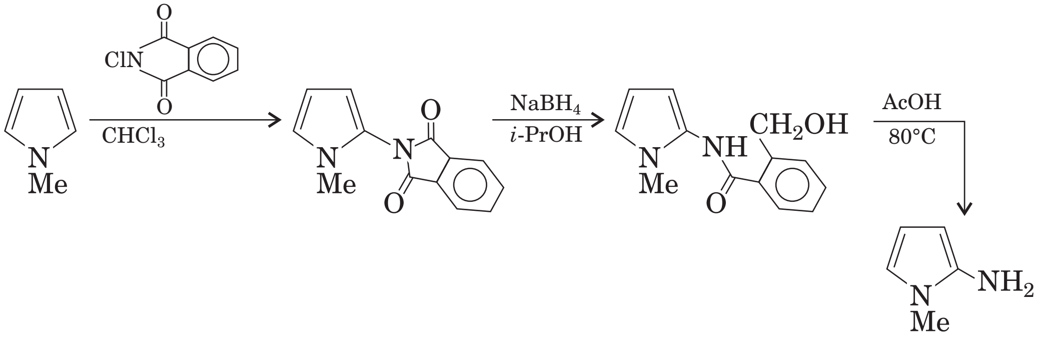
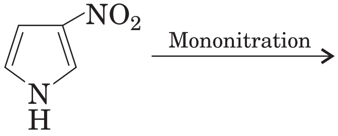
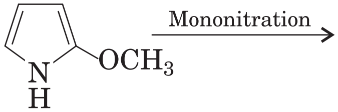
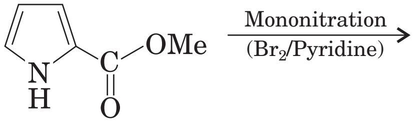


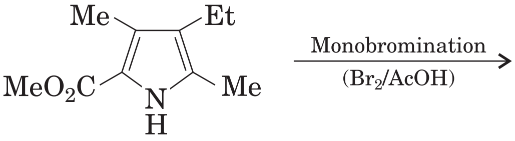
(d) 

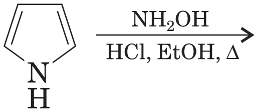
15. Predict the products and explain their formation:

(a) 

(b) 

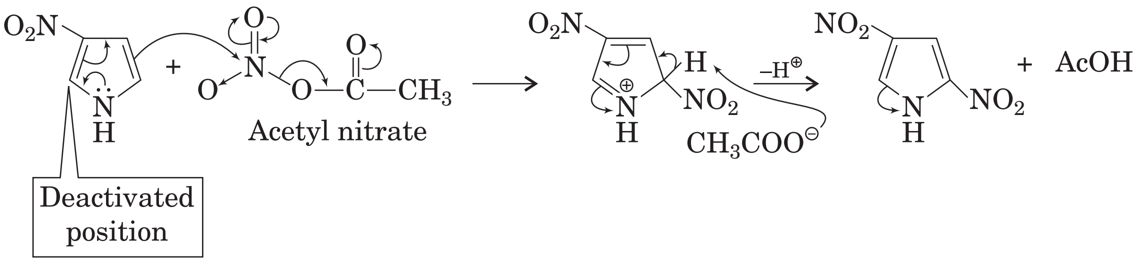
(c) 

(d) 

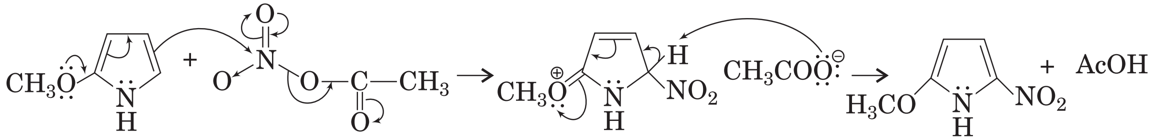
(e) 

Solution

(a) α-Attack by the electrophile occurs (not *ortho* to the electron-attracting —NO_2 group) to give 2,4-dinitropyrrole.

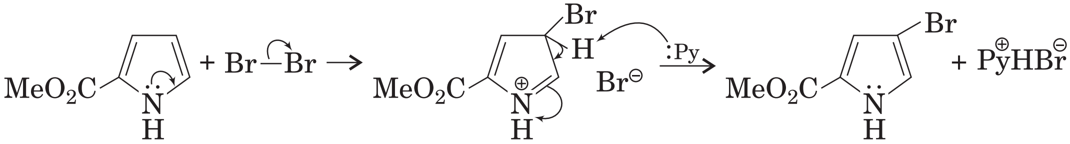


(b) The five-position (*para* to the —OCH_3 group) is activated both by the ring nitrogen and the —OCH_3 group (a +R group). For this reason, α attack occurs to yield 2-methoxy-5-nitropyrrole.

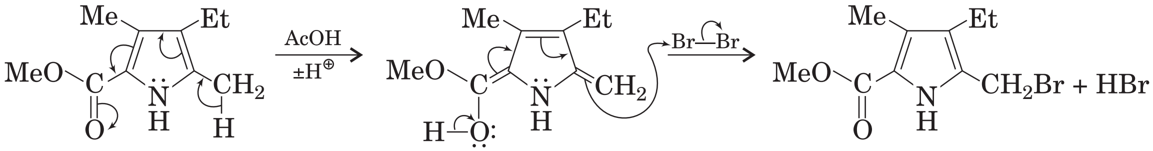


Acetyl nitrate

(c) The *meta*-directing effect of the ester group overcomes the normally dominant tending for *o*-substitution.



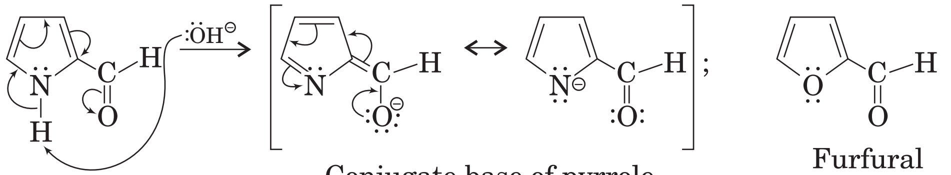
(d) An ester group can also activate a side-chain alkyl for halogenation.



(e) See **article no. 6.2.1.2** (ring cleavage reaction)

16. Furan-2-carbaldehyde or furfural, when treated with concentrated alkali, undergoes Cannizzaro reaction. However, when pyrrole-2-carbaldehyde is treated with concentrated alkali, it does not undergo the Cannizzaro reaction. Explain these observations.

Solution When pyrrole-2-carbaldehyde is treated with alkali, its conjugate base is formed in which the carbonyl group is highly deactivated, i.e., the partial positive charge on carbonyl carbon is considerably reduced, by resonance involving the negative nitrogen.



Conjugate base of pyrrole-2-carbaldehyde

Furfural or furan-2-carbaldehyde

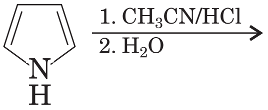
In furfural, on the other hand, the highly electronegative oxygen atom is very much reluctant to contribute its unshared pair of electrons for an effective resonance interaction with the carbonyl group. Therefore, the carbonyl carbon of this aldehyde is considerably positive.

For this reason, furfural undergoes the Cannizzaro reaction (involving nucleophilic attack by $OH^{\ominus}$ on the carbonyl carbon), whereas pyrrole-2-carbaldehyde does not.

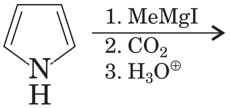
STUDY PROBLEMS

1. Pyrrole is less basic than a secondary aliphatic amines $(R_2\ddot{N}H)$—Why?
2. Predict the product expected to be formed in each of the following reactions:

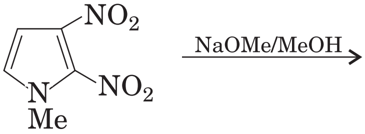
(a)



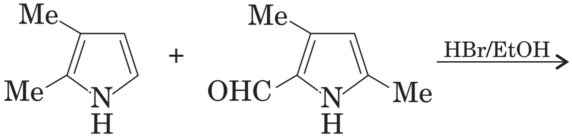
(b)



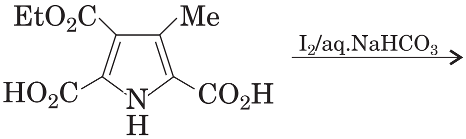
(c)



(d)



(e)

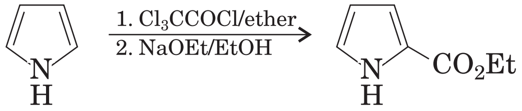


3. Why does pyrrole-2-carbaldehyde not undergo the Perkin reaction?
4. Pyrrole does not undergo the Diels–Alder reaction with DMAD; however, *N*-*p*-nitropheylpyrrole does. Explain these observations.
5. Explain the following observations:
   (a) Electrophilic substitution of pyrrole is easier than benzene.
   (b) Pyrrole reacts with KOH to form potassium salt.
   (c) Pyrrole does not form salts by protonation on nitrogen.
   (d) Treatment of 2,5-dimethylpyrrole with Zn/HCl gives a mixture of two isomeric products ($C_6H_{11}N$).
   (e) Pyrrole carboxylic acids readily decarboxylate on heating.
   (f) Pyrrole ($pK_a \simeq 17$) is a much stronger acid than NH_3 ($pK_a \simeq 36$).
   (g) Pyrrole shows resemblances to phenol.
   (h) Pyrrole is protonated on an α-carbon rather than on nitrogen.
   (i) Pyrrole is more reactive than furan so far as electrophilic substitution is concerned.

6. How would you distinguish between pyrrole and pyridine?

7. Write a curved-arrow mechanism for each of the following transformations:

(a)



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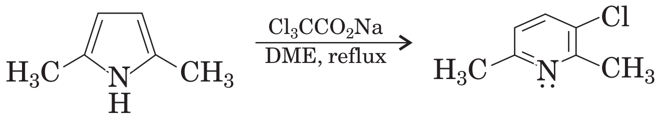

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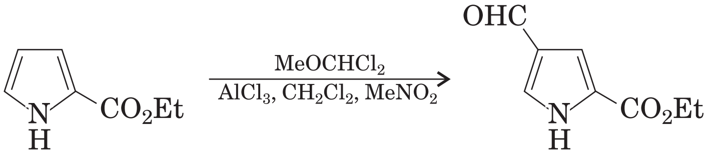
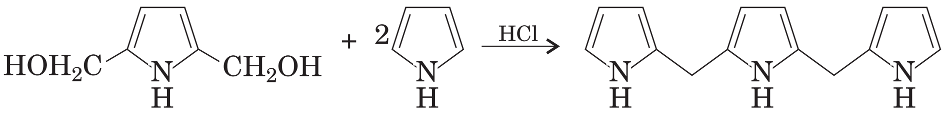


(d)



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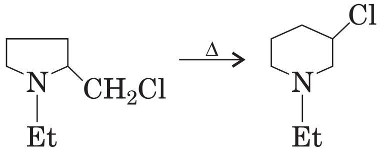
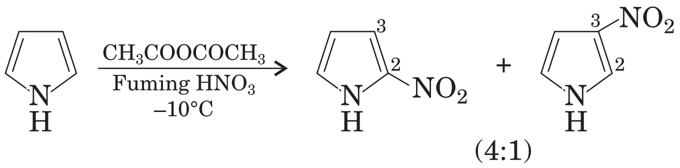
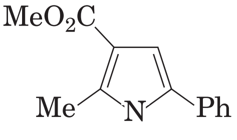


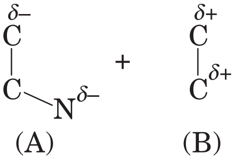
8. Explain the following observation:



What strategy would you take to get 3-nitropyrrole as the major product?

9. Outline the synthesis of from the compounds having the following skeletal units:

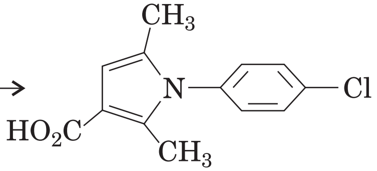




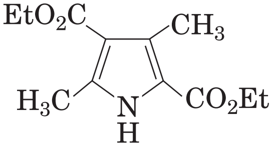
Provide the synthesis of the compounds corresponding to the skeletal units (A) and (B) from easily accessible starting materials.

10. Carry out the following conversions. Write the reaction conditions and the reagents involved.

(a) EAA $\longrightarrow$

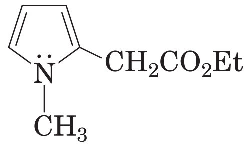


(b) EAA $\longrightarrow$



(c) Pyrrole $\longrightarrow$ Butanedial oxime

(d) *N*-Methylpyrrole $\longrightarrow$



11. When $MeCOCH_2CO_2Et$ is allowed to react with HNO_2 followed by addition of Zn/AcOH and pentane-2,4-dione, a pyrrole derivative ($C_{11}H_{15}NO_3$) is obtained. Write its structure and give the mechanism for its formation. Suggest a route whereby it could be converted into 2,4-dimethyl-3-ethylpyrrole.

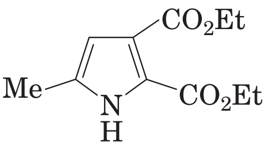
12. When 2-methylpyrrole is treated with HCl a dimer, not a trimer as does pyrrole itself, is obtained. Predict the structure of the dimer and explain why a trimer is not formed.

13. When 1-methoxycarbonylpyrrol is heated with DMAD at 160°C, diethyl 1-methoxycarbonylpyrrol-3,4-dicarboxylate is obtained. Suggest a reasonable mechanism for the reaction.

[**Hint:** A Diels–Alder reaction followed by a retro-Diels–Alder reaction in which acetylene is formed as one of the products.]

14. Suggest synthesis for each of the following pyrrole derivatives:

(a)



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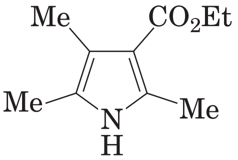
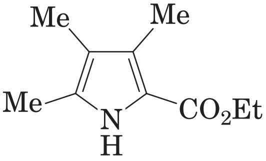
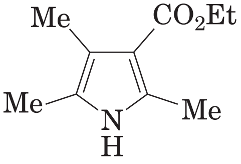


(c)



(d)



15. Give structures for compounds A—H:

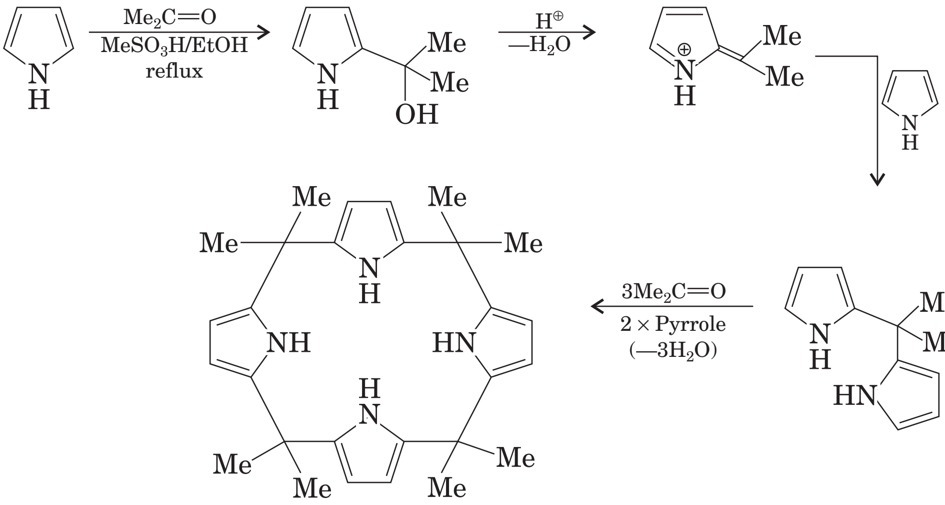
(a) $\text{Pyrrole} \xrightarrow{Cl_3CCOCl} A \xrightarrow{Br_2} B \xrightarrow[MeOH]{NaOMe} C$

(b) $\text{Pyrrole} \xrightarrow[DMF]{POCl_3} D \xrightarrow[AlCl_3]{MeCOCl} E \xrightarrow{aq.\ NaOH} F$

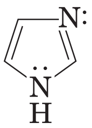
(c) $\text{1-Methylpyrrole} \xrightarrow[THF]{n\text{-BuLi}} [G] \xrightarrow{EtI} H$

16. Give the product of the reaction between pyrrol and excess acetone in acedic conditions. **[C.U. 2014]**

[**Hint:**



17. Arrange the following compounds in order of decreasing reactivity towards electrophilic aromatic substitution and give your reasoning.



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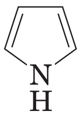

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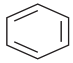
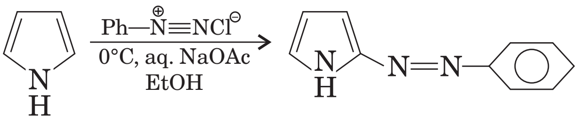


18. Starting from pyrrole how would you prepare: (i) 2-bromopyrrole, (ii) 3-bromopyrrole, (iii) 3-nitropyrrole and (iv) 4-formylpyrrole?

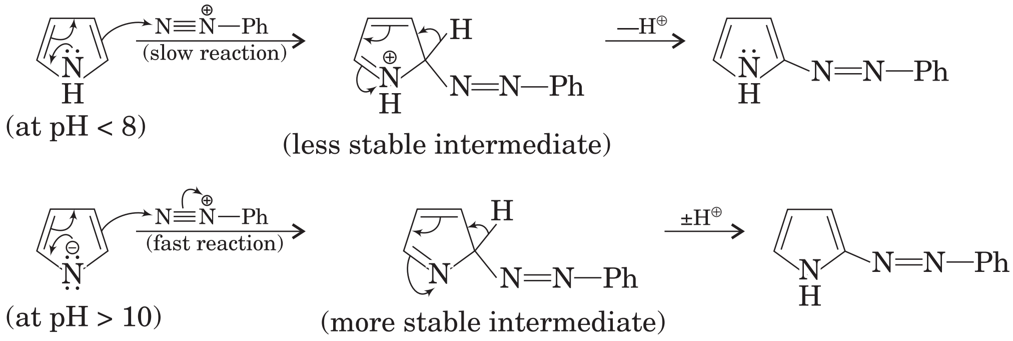
19. Which synthetic method and what reactants would be appropriate for the synthesis of a pyrrole derivative carrying —$CH(CH_3)CO_2CH_3$ group on nitrogen?

20. Consider the following reaction:



Compare the rate of the reaction at two different pH : one in pH < 8 and other in pH > 10.

[**Hint:** Pyrrole gives a mono-azo derivative by reacting as a neutral species below pH 8. However, it reacts with diazonium ion 10^8 times faster in solutions above pH 10. This is because in alkaline medium, it reacts by way of the pyrrole anion which is more nucleophilic than neutral pyrrole.



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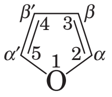
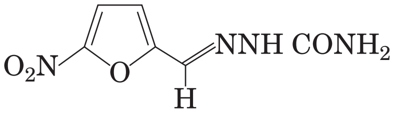
6.2.2 Furan and Its Derivatives

The chemistry of furan (*furfuran*) itself started with the discovery of compounds containing furan ring. The aromatic furan ring occurs especially in terpenoids. Furan is obtained when wood especially the pine wood, is distilled. Furan-2-carboxylic acid (furoic acid) was first obtained by Scheele in 1780 by dry distillation of mucic acid. Furan was obtained later by heating furoic acid at its boiling point. It is most conveniently prepared by decarboxylating furoic acid in quinoline in the presence of copper powder. There are two monosubstituted and four disubstituted derivatives of furan.

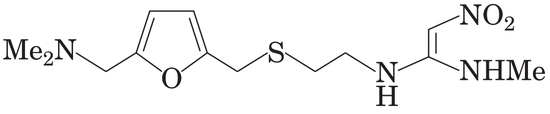


Furan

Furan is commercially important due to its role as the precursor of tetrahydrofuran (THF), a widely used solvent. Some 5-nitrofurfural derivatives are important in medicine. Nitrofurazone, for example, is a well-known bactericide. Ranitidine, used for the treatment of stomach ulcers, is one of the most commercially successful medicines ever developed.



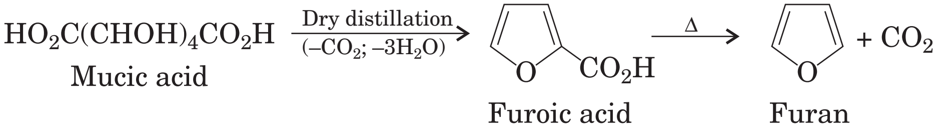
Nitrofurazone



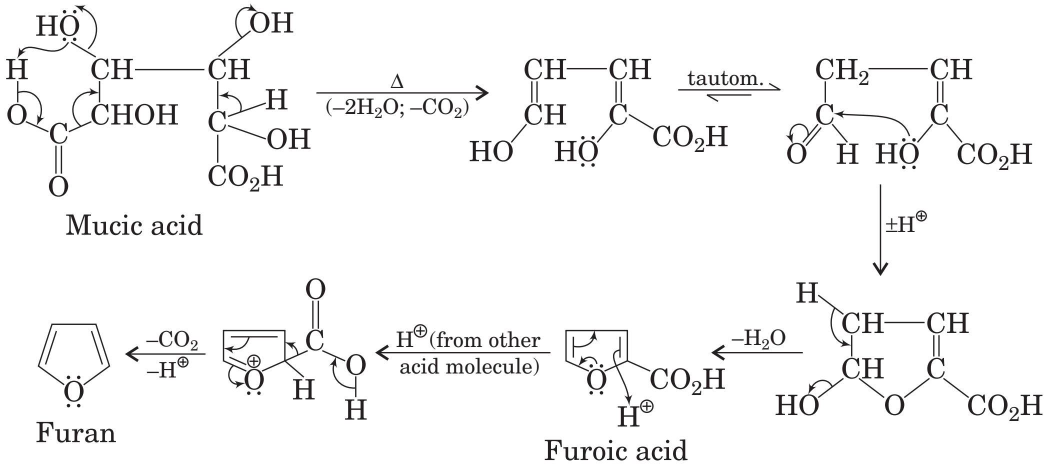
Ranitidine

6.2.2.1 *Synthetic Methods*

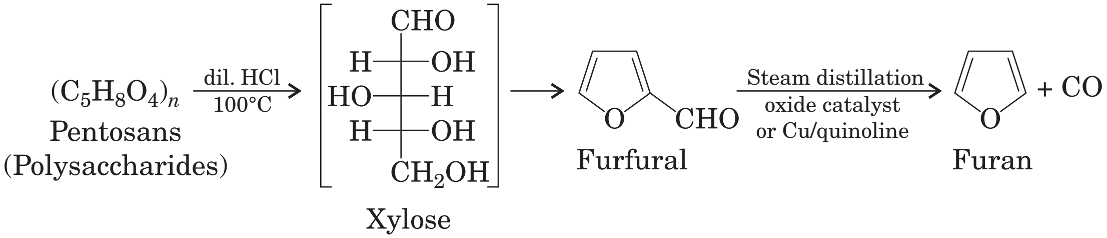
1. From mucic acid Furan can be prepared by the dry distillation of mucic acid followed by heating the product furoic acid at its b.p.



Mechanism of the reactions

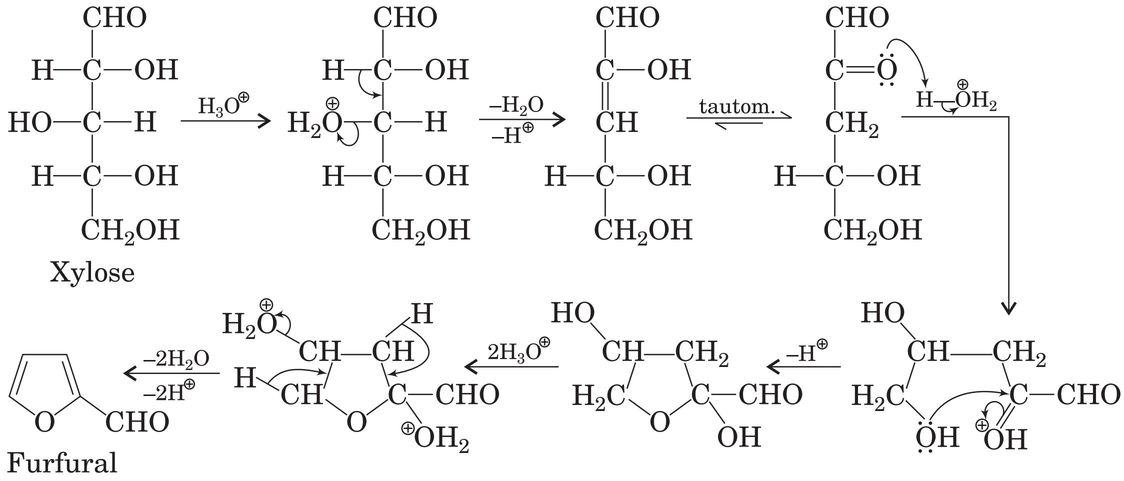


2. From Carboxyhydrates Furan is commercially prepared by decarbonylation of furfural. Furfural is manufactured from xylose, obtained in turn from pentosans (which are polysaccharides extracted from plants, e.g., oat hulls, corn cobs and rice husks) by acid-catalyzed hydrolysis.

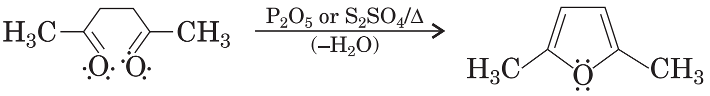


Mechanism of the reaction

Xylose undergoes dehydration and cyclization to yield furfural through the steps as follows:



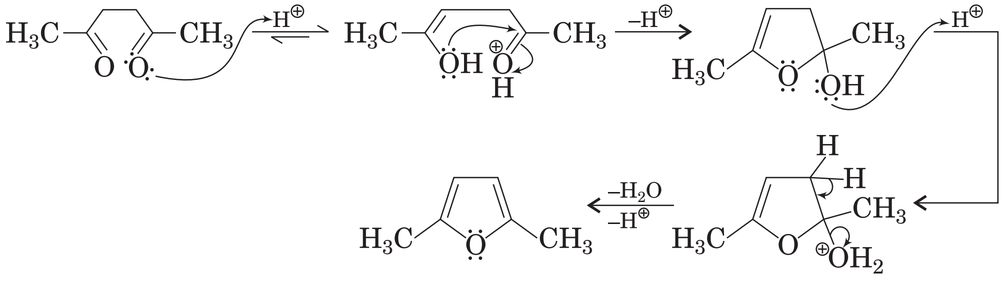
3. Paal–Knorr synthesis It is a general method for synthesizing furan derivatives and it involves dehydration of an enolizable 1,4-dicarbonyl compound by using reagents such as phosphorus pentoxide, sulphuric acid, etc. 2,5-Dimethylfuran, for example, can be prepared by heating acetonylacetone (hexane-2,5-dione) with P_2O_5 or conc. H_2SO_4.



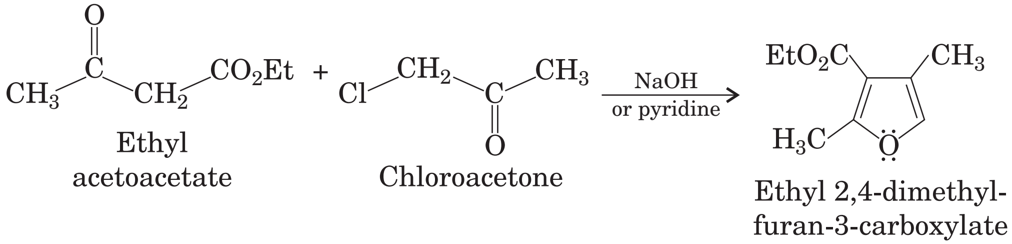
Acetonylacetone 2,5-Dimethylfuran

Mechanism of the reaction

The process involves addition of the enol oxygen at one carbonyl group to the other carbonyl group, then elimination of a molecule of water.

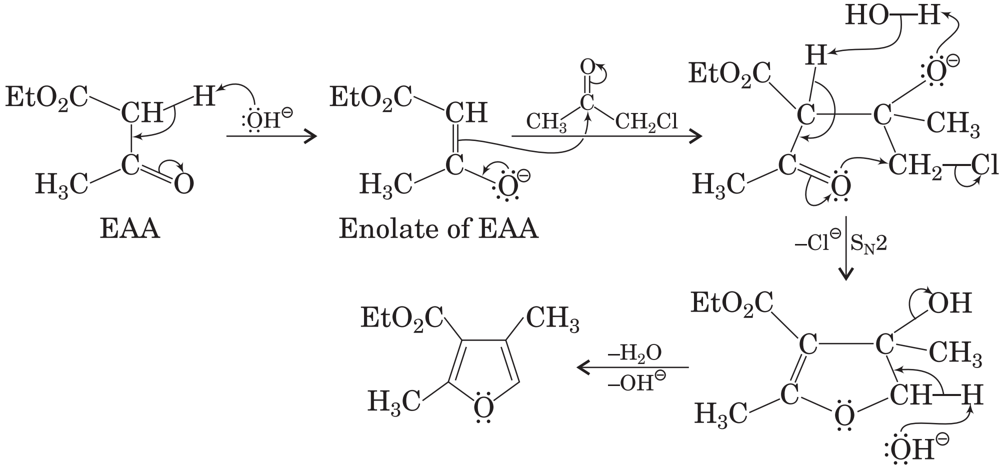


4. Feist–Benary synthesis This classical synthesis involves an aldol condensation of an α-haloketone (or an α-haloaldehyde) with a β-keto ester (or a β-diketone) in the presence of sodium hydroxide or pyridine. The ring closure is achieved *via* intramolecular displacement of halide by the enolate oxygen. Ethyl 2,4-dimethylfuran-3-carboxylate, for example, can be prepared by treating ethyl acetoacetate and chloroacetone in the presence of NaOH or pyridine.

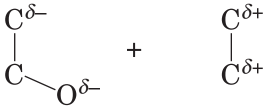


Ethyl acetoacetate Chloroacetone Ethyl 2,4-dimethylfuran-3-carboxylate

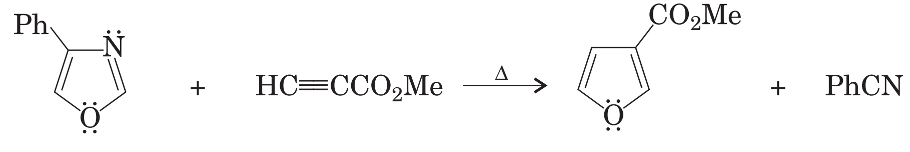
Mechanism of the reaction



The Feist–Benary synthesis is, in fact, a combination of the following two aliphatic skeletal fragments:

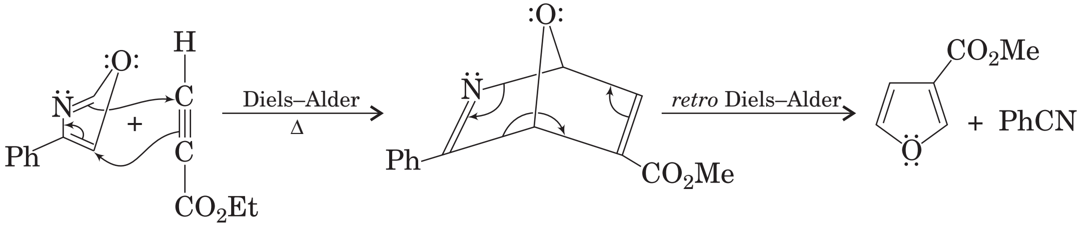


5. From other heterocyclic systems Oxazoles react with acetylenic dienophiles to give Diels–Alder adducts which subsequently undergo retro Diels–Alder reaction to yield furans. For example:



4-Phenyloxazole Methyl propynoate Methyl furan-3-carboxylate

Mechanism of the reaction

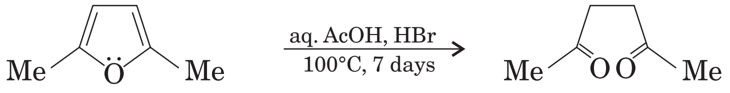


6.2.2.2 *Properties and Reactions*

Furan is a colourless liquid with odour like chloroform. Its boiling point is 32°C and it is soluble is most of the organic solvents. Furan has a resonance energy of 16 kcal/mol. Of the three five-membered systems with one heteroatom considered in this chapter, furan is the 'least aromatic'. The lower aromaticity of furans also manifests itself in a much greater tendency to undergo cycloadditions, as a 4π diene component in Diels–Alder reactions. In fact, furans are much more like dienes, and less like a six electron aromatic system, than are pyrroles and thiophenes.

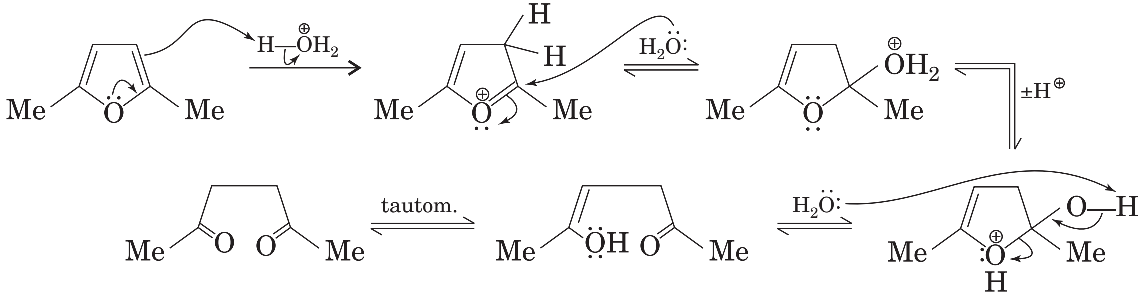
Some important reactions of furans are as follows:

1. Reactions of protonated furans The hydrolysis of furans involves nucleophilic addition of water to an initially formed cation, giving rise to open-chain 1,4-dicarbonyl compounds. This is in effect the reverse of one of the general methods for the construction of furan ring (the Paal–Knorr synthesis). Succinaldehyde cannot be obtained from furan itself because this dialdehyde is very reactive under conditions for hydrolysis. However, some alkylfurans can be efficiently converted into 1,4-dicarbonyl products. For example:



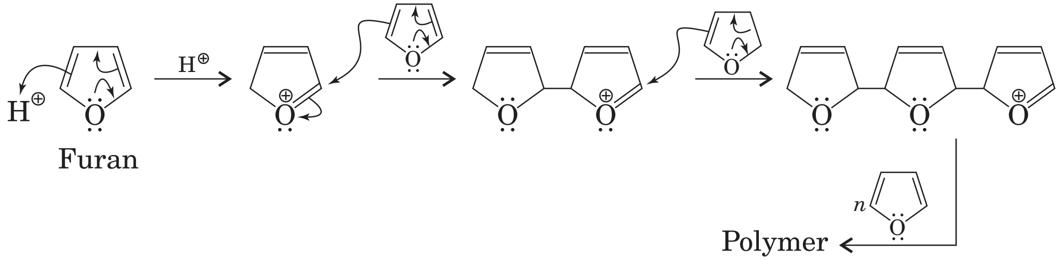
2,5-Dimethylfuran Hexane-2,5-dione

Mechanism of the reaction (hydrolysis)

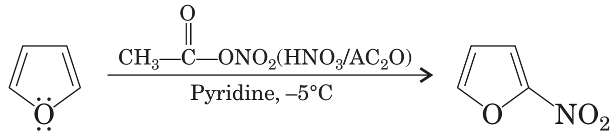


2. Electrophilic Substitutions Furan being a π-excessive heterocycle undergoes electrophilic substitution with exceptional case (6×10^{11} times faster than benzene). However, the conditions under which electrophilic substitutions are carried out need to be carefully controlled. Furthermore, the mechanism of the reaction is often not so simple as that of the benzenoid system.

(i) Nitration Furan cannot be nitrated directly because it undergoes ready polymerization in the presence of concentrated acids.

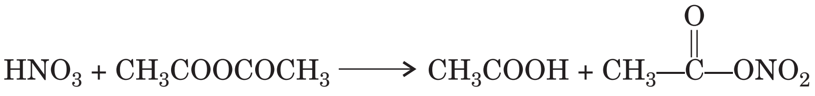


Nitration of furan is usually carried out with the mild nitrating agent acetyl nitrate, CH_3COONO_2 (a mixture of acetic anhydride and nitric acid) at –5 to 30°C to yield 2-nitrofuran. The reaction proceeds by the addition-elimination mechanism. A non-aromatic adduct is formed by the electrophilic attack at C-2 followed by the nucleophilic attack of acetate ion to the cationic intermediate, usually at C-5. Aromatization, by the loss of AcOH, to give 2-nitro-substitution product takes place under solvolytic conditions. However, it can be better effected by the treatment with the weak base pyridine.



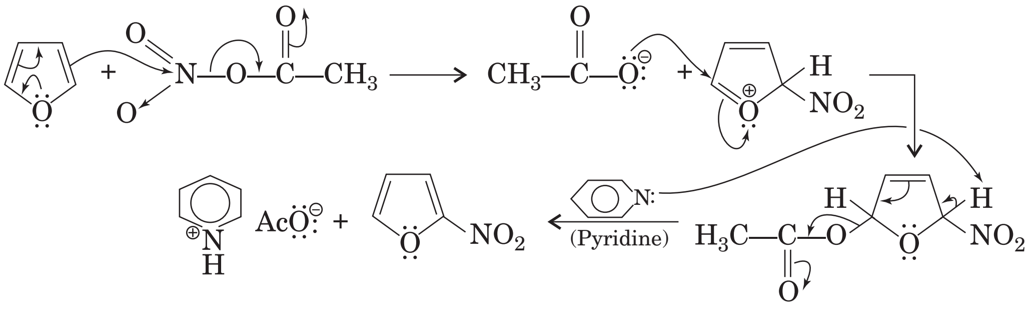
Furan 2-Nitrofuran

Mechanism of the reaction

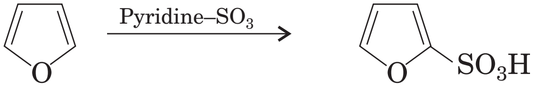


$$HNO_3 + \underset{\text{Acetic anhydride}}{CH_3COOCOCH_3} \longrightarrow CH_3COOH + \underset{\text{Acetyl nitrate}}{CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-ONO_2}$$

Acetic anhydride Acetyl nitrate

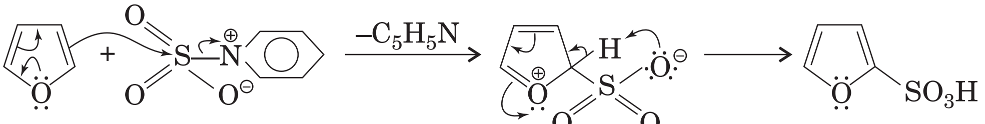


(ii) Sulphonation Furan like pyrrole undergoes resinification in the presence of sulphuric acid. However, it can be smoothly sulphonated by pyridine–SO_3 complex to give furan-2-sulphonic acid in very good yield (90%).



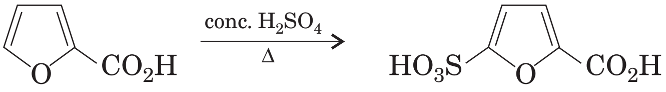
Furan Furan-2-sulphonic acid

Mechanism of the reaction



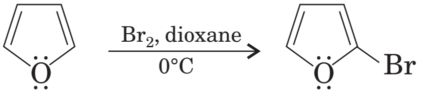
Furan Pyridine –SO_3 complex

If a –I group is present in the ring, then sulphonation can be carried out directly, e.g., furoic acid gives furoic-5-sulphonic acid when treated with conc. H_2SO_4.

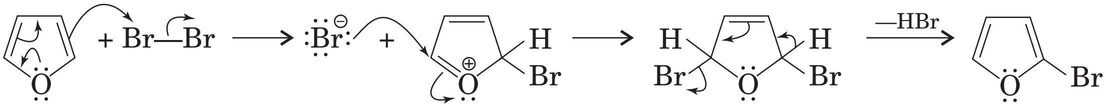


Furoic acid Furoic-5-sulphonic acid

(iii) Halogenation Furan reacts vigorously with chlorine and bromine at room temperature to give polyhalogenated products or resins, but does not react at all with iodine. When bromination is carried out in dioxane at 0°C (a carefully controlled condition), a 1,4-dibromo-1,4-dihydroadduct is formed which subsequently eliminates a molecule of HBr to yield 2-bromofuran.

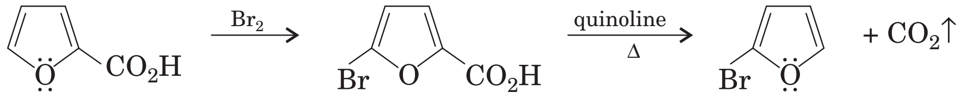


Mechanism of the reaction



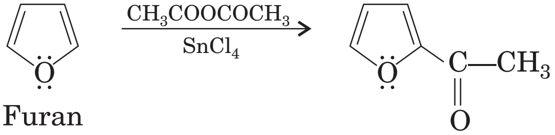
Treatment of furan with Cl_2 in dichloromethane at –40°C yields 2-chlorofuran predominantly.

Since halogen acids liberated during the halogenation of furan cause polymerization, halogenated furans are often obtained through an indirect process involving halogenation of furoic acid followed by decarboxylation of the product. For example:



Furoic acid 5-Bromofuroic acid 2-Bromofuran

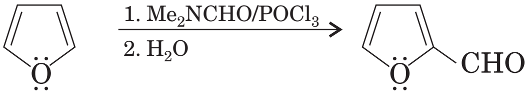
(iv) Friedel–Crafts reaction Acid anhydrides or acyl halides normally react with furans in the presence of Lewis acid catalysts, like $ZnCl_2$ or $SnCl_4$ to yield 2-acylfuran. A better catalyst for the reaction with anhydrides is BF_3 in ether (the reagent is the complex $Et_2O \rightarrow BF_3$).



Furan 2-Acetylfuran

The Friedel–Crafts alkylation is not so successful partly because of polymerization caused by the catalyst and partly because of polyalkylation.

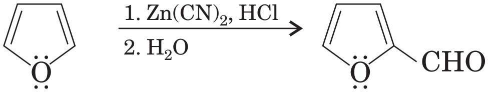
(v) Vilsmeier–Haak formylation When furan is treated with $POCl_3$ and DMF and the resulting salt is hydrolyzed, furfural is obtained.



Furan Furfural

For mechanism of the reaction see **article 6.2.1.2**.

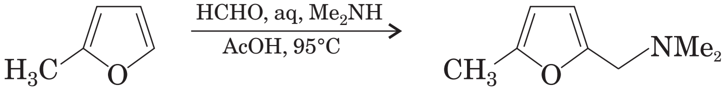
(vi) Gattermann reaction Furan undergoes the Gattermann reaction to form furfural.



Furan Furfural

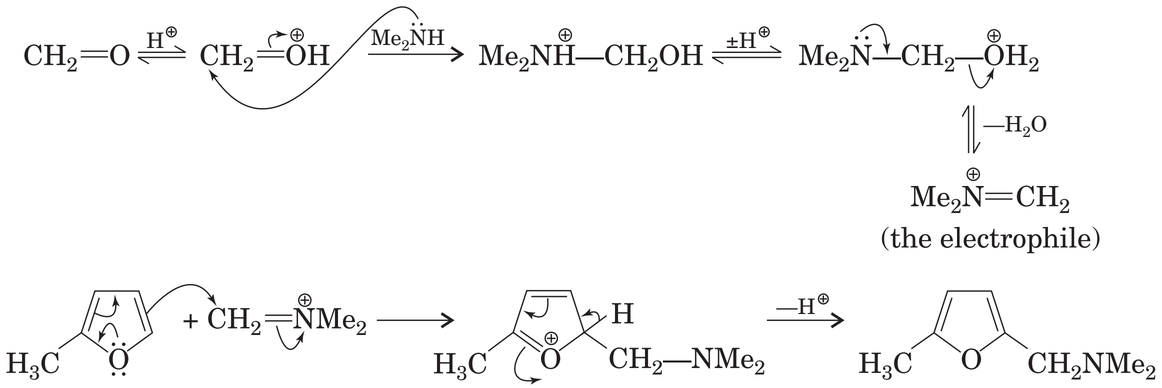
For mechanism of the reaction see **article 6.2.1.2**.

(vii) Mannich reaction Monoalkylfurans undergo the Mannich reaction normally. For example:



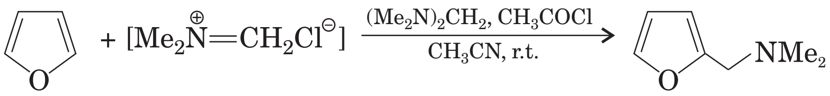
2-Methylfuran

Mechanism of the reaction



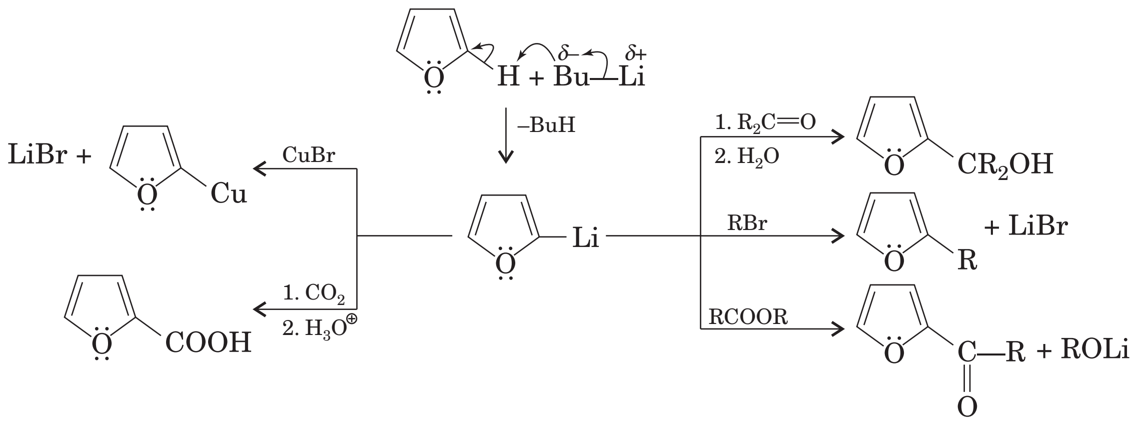
$CH_2{=}O \overset{H^\oplus}{\rightleftharpoons} CH_2{=}\overset{\oplus}{O}H \xrightarrow{Me_2\ddot{N}H} Me_2\overset{\oplus}{N}H{-}CH_2OH \overset{\pm H^\oplus}{\rightleftharpoons} Me_2\ddot{N}{-}CH_2{-}\overset{\oplus}{O}H_2$
—H₂O
$Me_2\overset{\oplus}{N}{=}CH_2$
(the electrophile)
H₃C
+ $CH_2{=}\overset{\oplus}{N}Me_2$
H
CH₂—NMe₂
—H⊕
CH₂NMe₂

The Mannich reaction of furan itself can be carried out with performed iminium salt to give 2-substitution product.

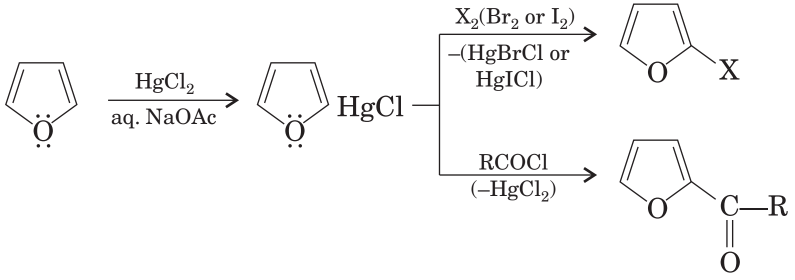


+ $[Me_2\overset{\oplus}{N}{=}CH_2Cl^\ominus]$
$(Me_2N)_2CH_2$, CH_3COCl
CH_3CN, r.t.
O
NMe₂

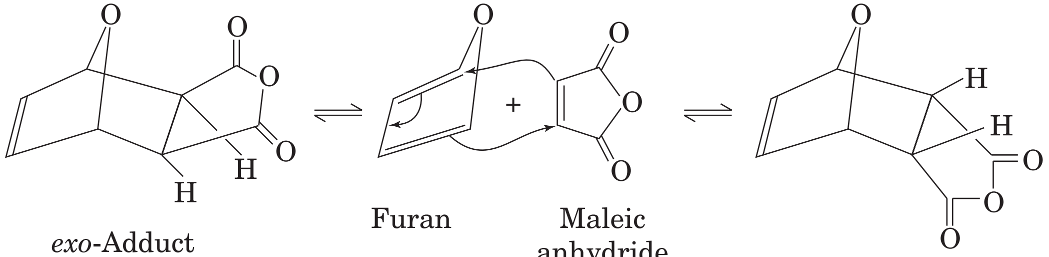
3. Metallation of furans Furan reacts with butyllithium to form the 2-lithium derivative. This reacts with other reagents to give useful products.



Furan undergoes ready mercuration at the 2-position. For example, when it is treated with mercuric chloride in aqueous sodium acetate, 2-chloromercurifuran is obtained. These mercuri-compounds are useful intermediates because the mercuri-group can be readily replaced by bromine or iodine, and by an acyl group.



4. Diels–Alder reaction As furan is least aromatic of the five-membered heterocycles (the highly electronegatigve oxygen atom is very much reluctant to share its unshared electron pair of maintaining aromatic sextet), it behaves as a diene in the Diels-Alder reaction. For example, when furan is allowed to react with maleic anhydride in ether at 25°C, the *exo*-adduct (the thermodynamic product) is obtained predominantly. In fact, the *endo*-adduct the kinetic product is formed at a faster rate (through a low-energy transition state involving secondary orbital interactions) and then equilibrates to give the more stable *exo*-adduct (the cycloaddition being easily reversible).



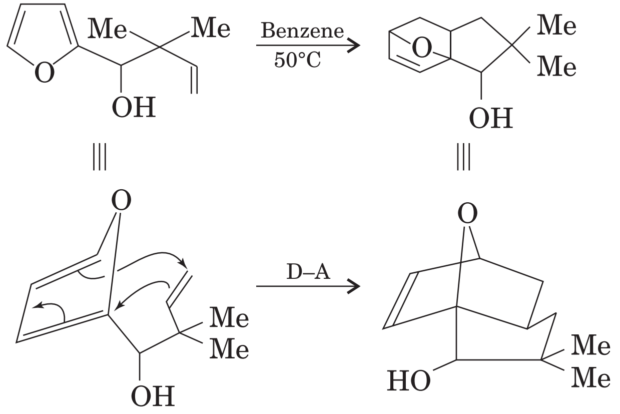
exo-Adduct
(80%)

Furan

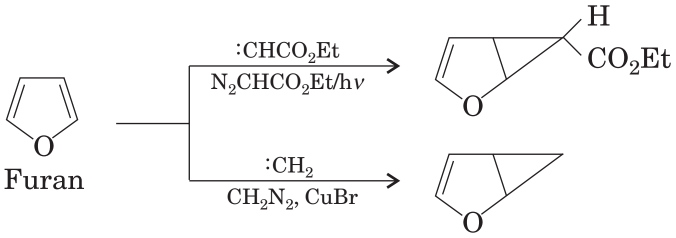
Maleic
anhydride

endo-Adduct
(20%)

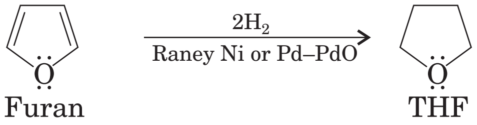
Properly substituted furans also undergo intramolecular Diels–Alder reaction to give the corresponding adduct. For example:



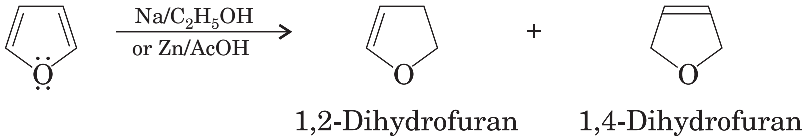
5. Reaction with carbenes Carbenes (generated in situ) add across the double bond in furan to yield cyclopropane derivatives. For example:



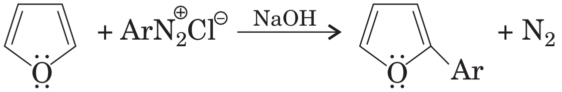
6. Reduction Catalytic reduction of furan yields tetrahydrofuran (THF), an industrially important solvent.



Reduction with Na/alcohol or Zn/AcOH leads to the formation of a mixture of 1,2- and 1,4-dihydrofuran.

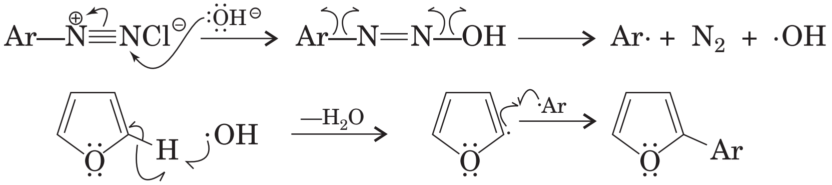


7. Gomberg reaction Furan undergoes the Gomberg reaction when treated with diazonium salts in alkali solution:



Mechanism of the reaction

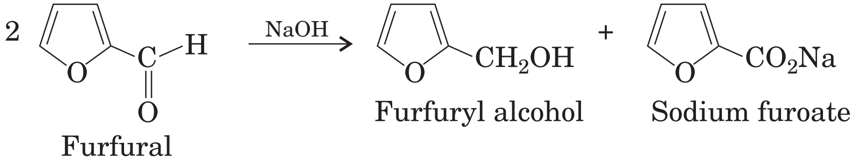
The reaction takes place by a free-radical mechanism.



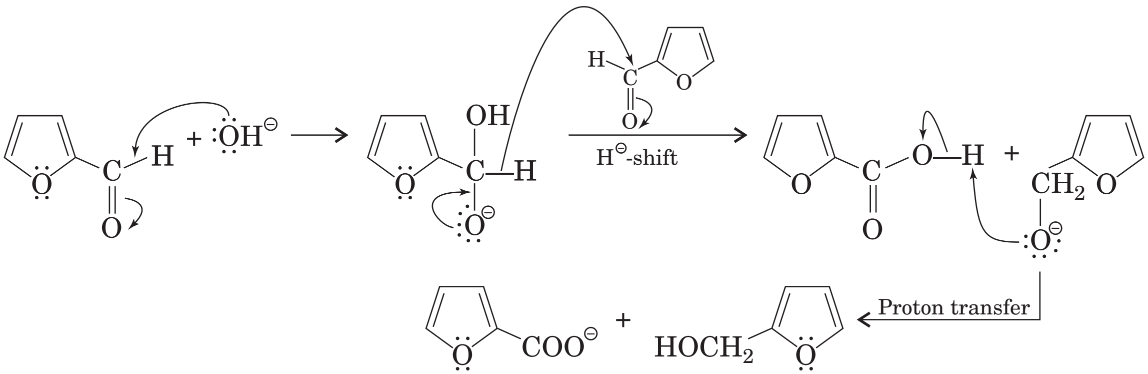
6.2.2.3 Reactions of furfural

Several furan derivatives are industrially very important. Notable among them is furfural (furfuraldehyde) which is widely used for the preparation of dyes, plastics, etc. It is also used as a solvent in synthetic rubber manufacture, and as an extraction liquid in petroleum refining. It is chemically very similar to benzaldehyde. Like benzaldehyde, it undergoes the Cannizzaro reaction, the benzoin condensation, the Claisen-Schmidt reaction and the Perkin reaction.

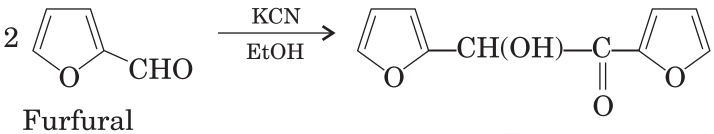
1. Cannizzaro reaction When treated with aqueous sodium hydroxide, furfural undergoes the Cannizzaro reaction leading to the formation of furfuryl alcohol and furoic acid (as sodium salt).



Mechanism of the reaction



2. Benzoin condensation When furfural is allowed to react with ethanolic potassium cyanide, furoin is obtained.

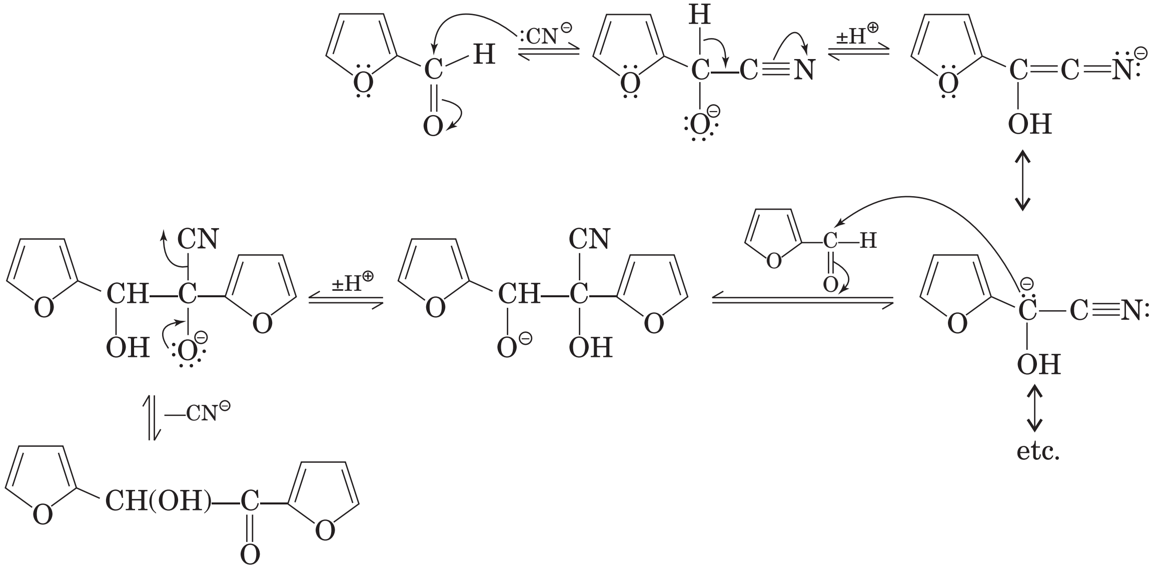


Furfural

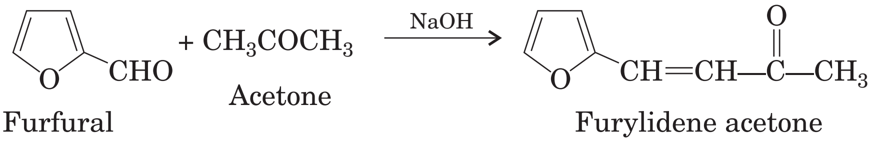
Fuiron

Mechanism of the reaction

The reaction which is completely reversible proceeds through the steps as follows:

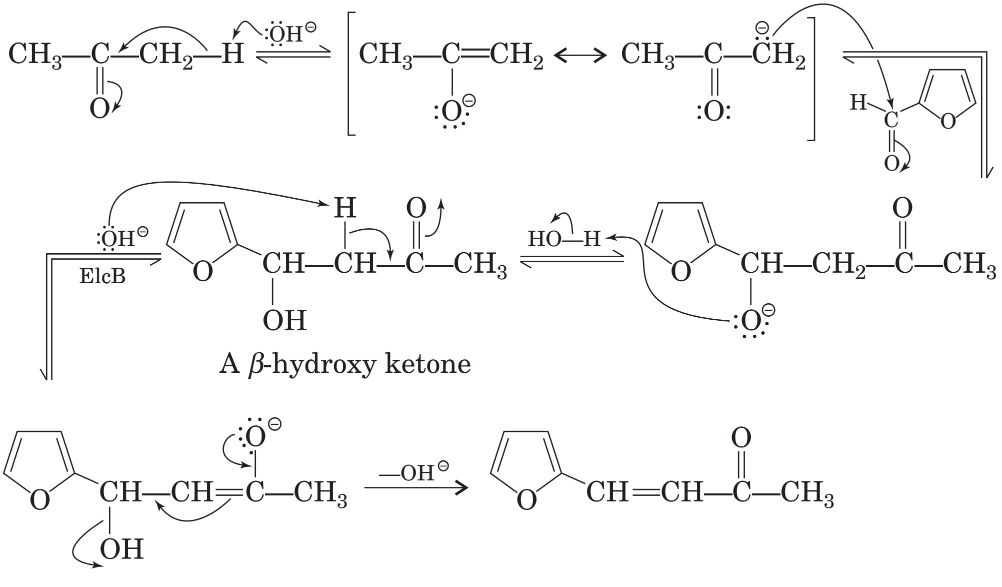


3. Claisen–Schmidt reaction When furfural is allowed to react with acetone in the presence of sodium hydroxide, furylidene acetone is obtained.



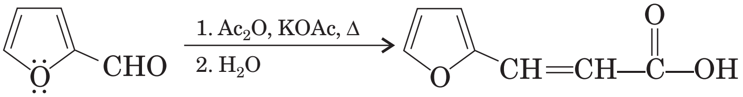
Mechanism of the reaction

This condensation reaction proceeds through the steps as follows:



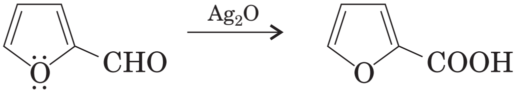
The enolate ion reacts with furfural to form a β-hydroxyketone which then undergoes base-catalyzed dehydration by E1cB mechanism to yield furylidene acetone.

4. Perkin reaction When furfural is treated with acetic anhydride in the presence of potassium acetate and the resulting mixed anhydride is hydrolyzed, furylacrylic acid is obtained.



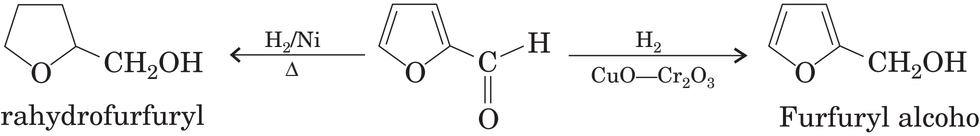
Furfural Furylacrylic acid

5. Oxidation Furfural undergoes oxidation with a mild oxidizing agent like Ag_2O to form furoic acid.



Furfural Furoic acid

6. Reduction On reduction with $H_2/CuO–Cr_2O_3$ and H_2/Ni it gives furfuryl alcohol and tetrahydrofurfuryl alcohol, respectively.



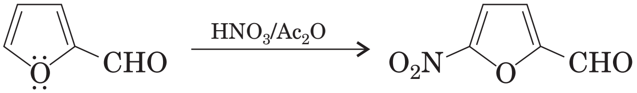
Tetrahydrofurfuryl alcohol

Furfural

Furfuryl alcohol

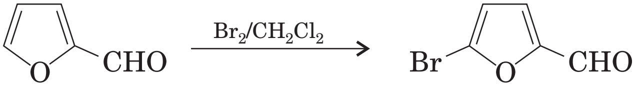
7. Electrophilic substitutions

Nitration:



(5-Nitrofurfural)

Bromination:

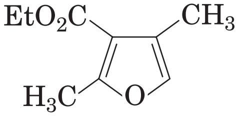


(5-Bromofurfural)

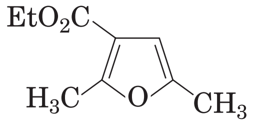
SOLVED PROBLEMS

1. **Explain why two isomeric products are formed from the same starting materials.**

(a) EAA + Chloroacetone $\xrightarrow{\text{aq. NaOH}}$

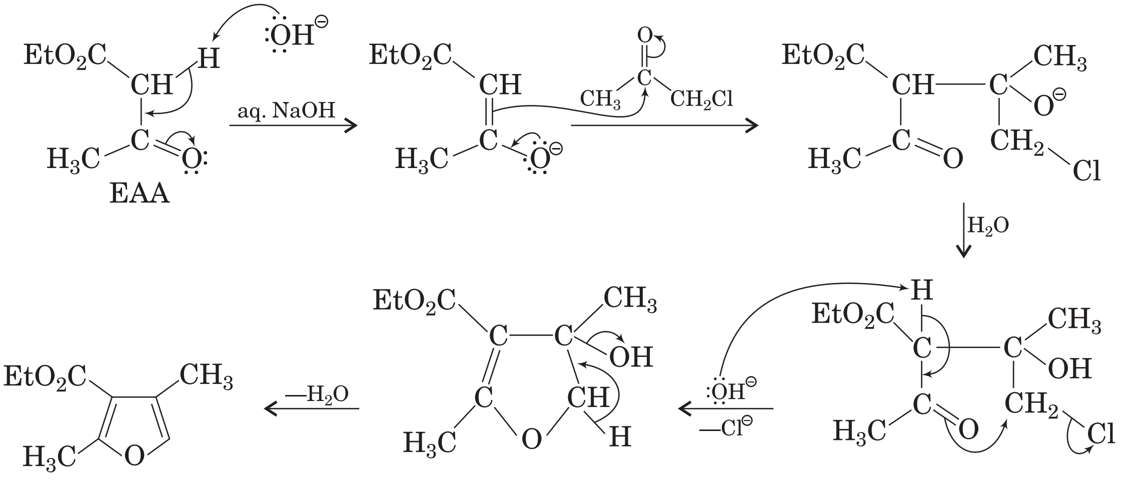


(b) EAA + Chloroacetone $\xrightarrow[\text{NaOH}]{\text{NaI/acetone}}$

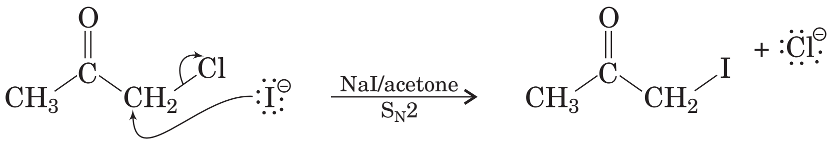


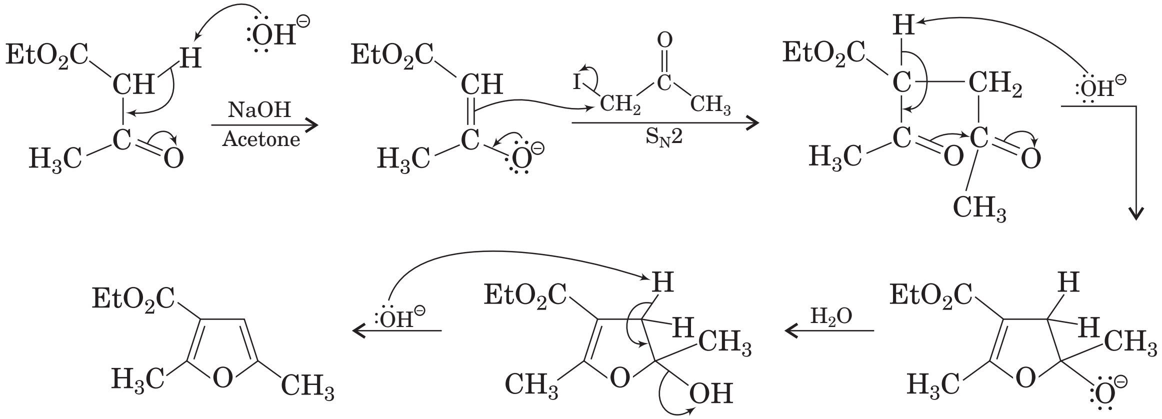
Solution

(a) In this aqueous medium, the usual S_N2 reaction between the enolate of ethyl acetoacetate and α-haloketone is arrested and an aldol reaction occurs preferentially. An intramolecular displacement of chlorine then occurs by the enolate oxygen to give, after loss of a molecule of water, ethyl 2,4-dimethylfuran-3-carboxylate.



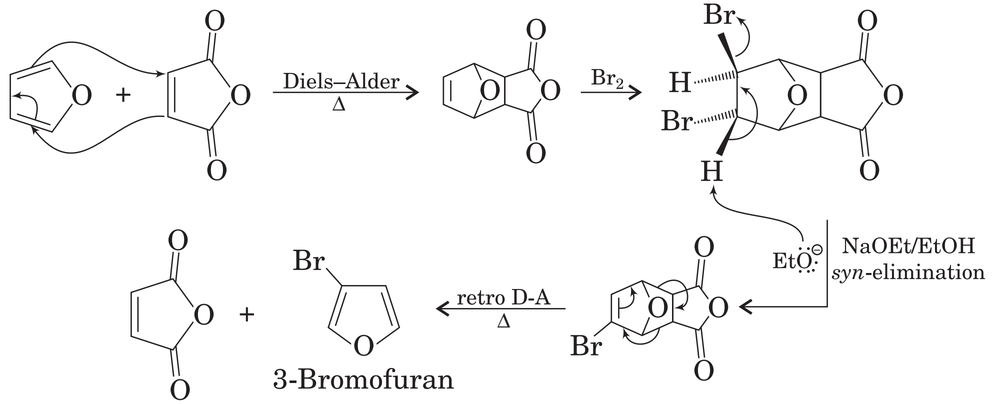
(b) Since acetone is a better S_N2 solvent, chloroacetone in first converted to iodoacetone. Iodoacetone then reacts with the enolate of EAA to yield a 1,4-diketone. Cyclization of the diketone then occurs to give ethyl 2,5-dimethylfuran-3-carboxylate.





2. How can 3-bromofuran be prepared from furan by using a Diels–Alder reaction and a *retro* Diels–Alder reaction?

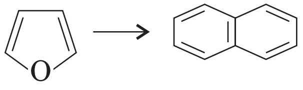
Solution 3-Bromofuran can be prepared from furan by carrying out the reactions as follows:



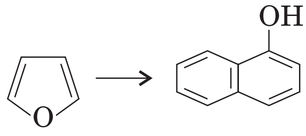
3-Bromofuran

3. How would you carry out the following transformations? Give mechanisms of the reactions involved. [C.U. 2013]

(a)



(b)



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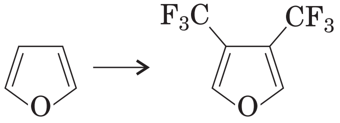

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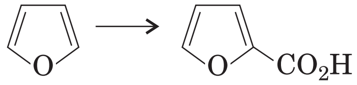

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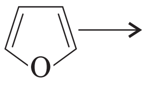
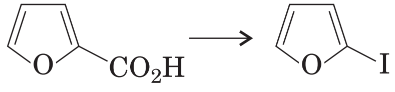
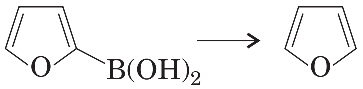
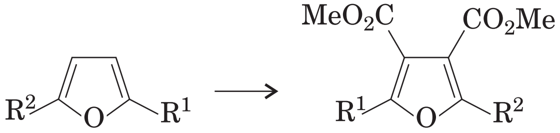


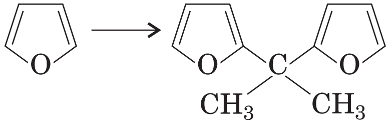
$\longrightarrow (MeO)_2CH(CH_2)_2CH(OMe)_2$

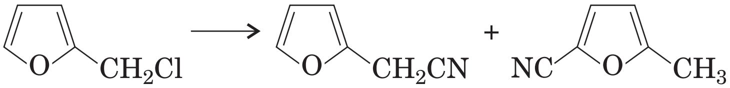
(f)



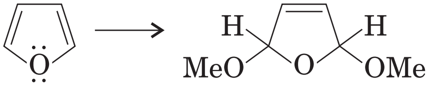
(g) 

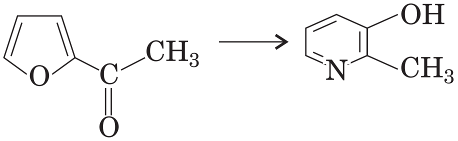
(h) 

(i) 

(j) 

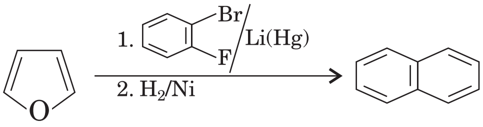
[C.U. 2012, 2014, 2015]

(k) 

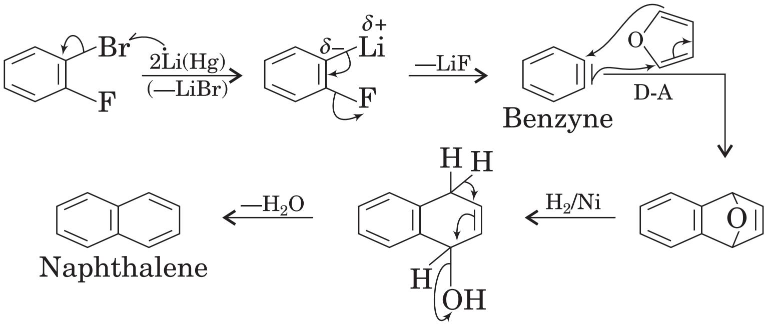
(l) 

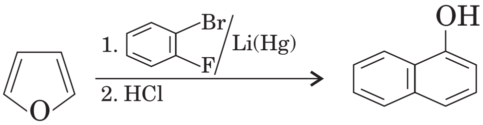
[C.U. 2013]

Solution

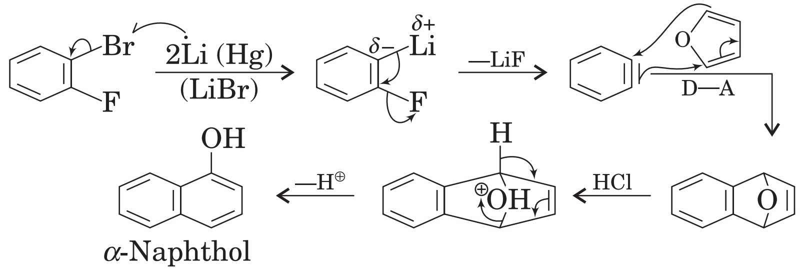
(a) 

Mechanism:



(b) 

Mechanism:



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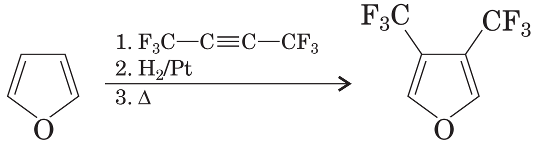

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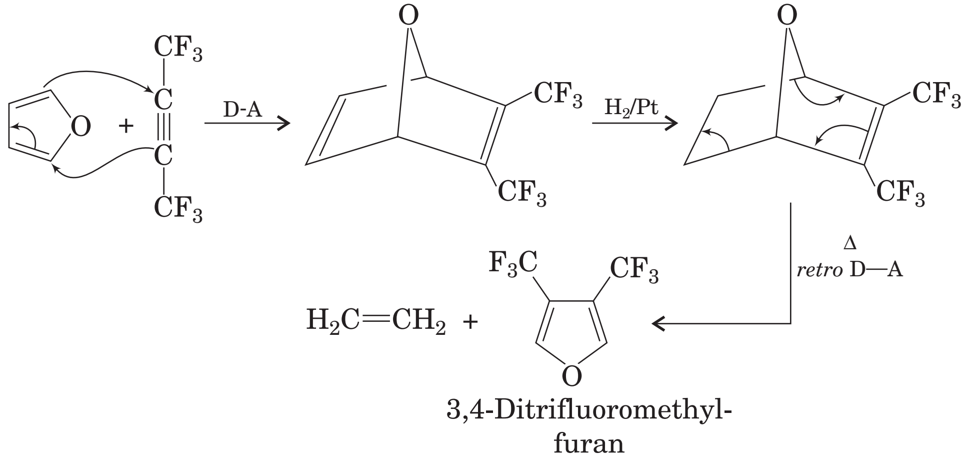
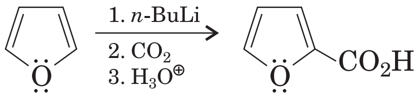


(d)



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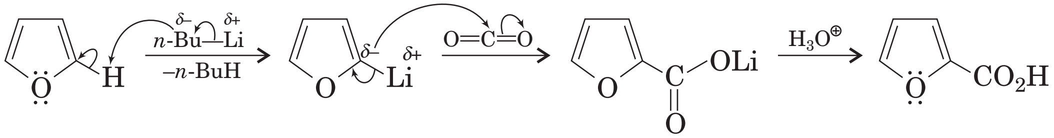

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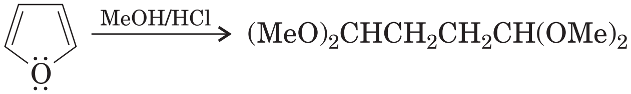

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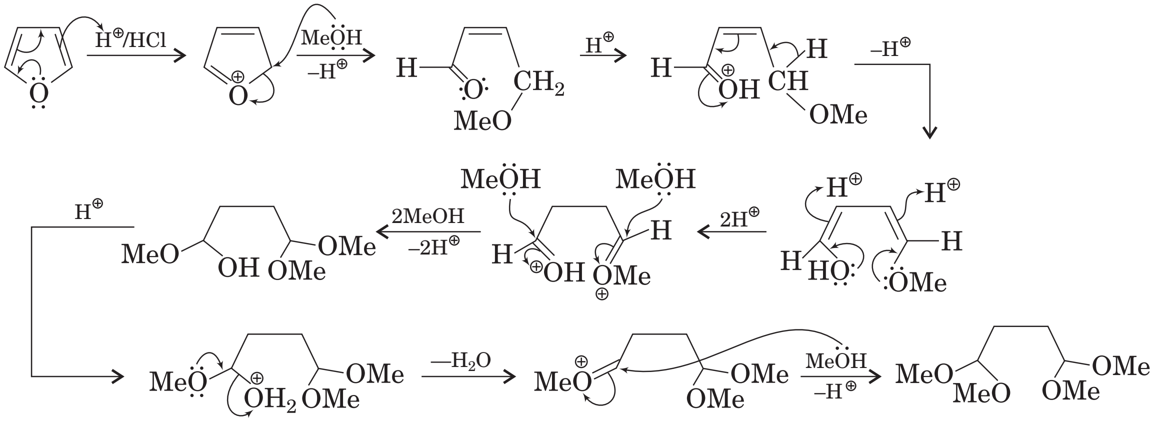

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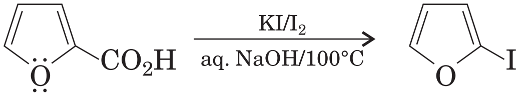

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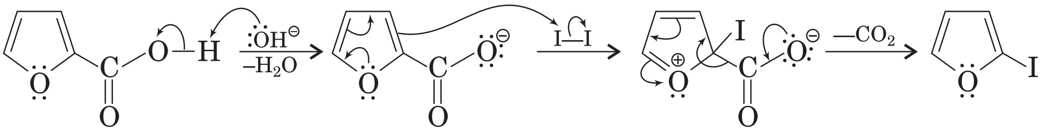

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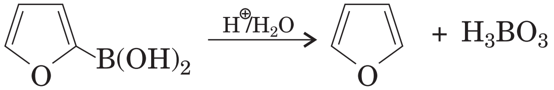

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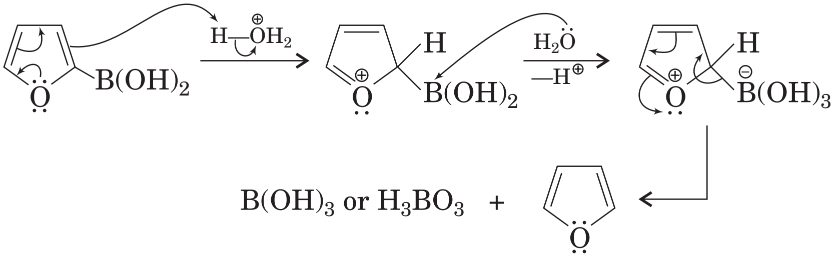

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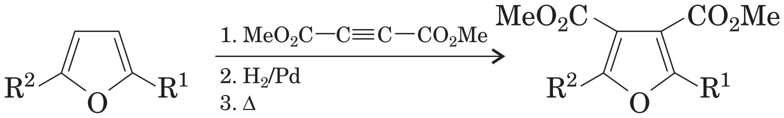

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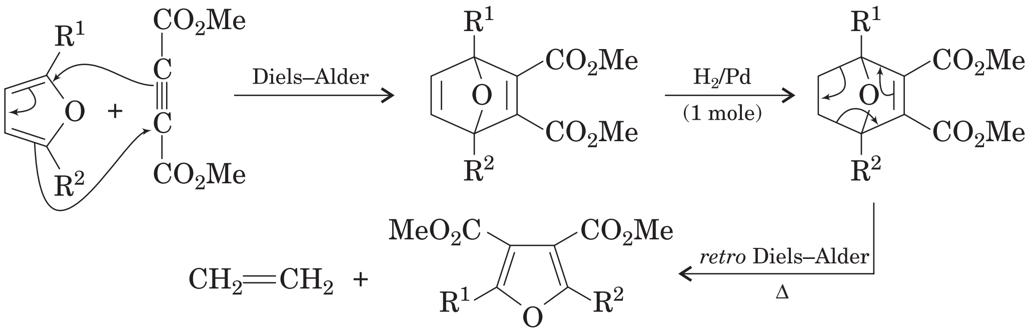

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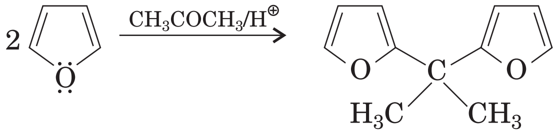

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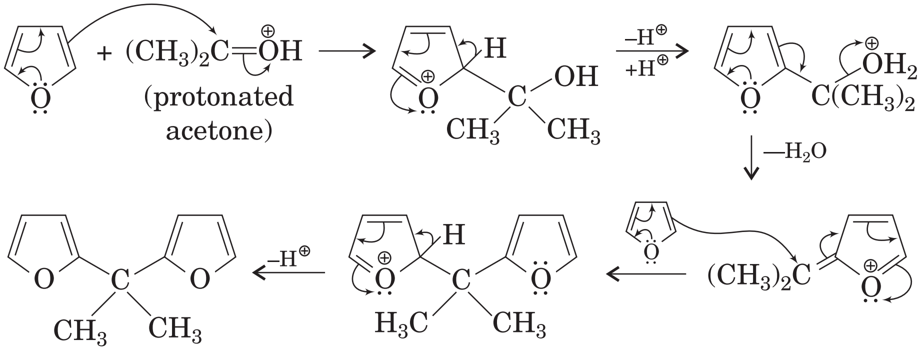

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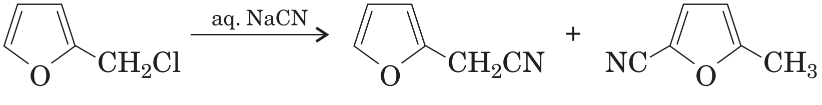

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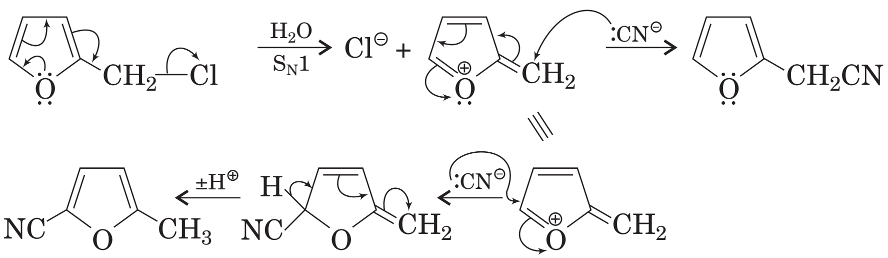

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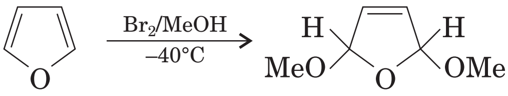

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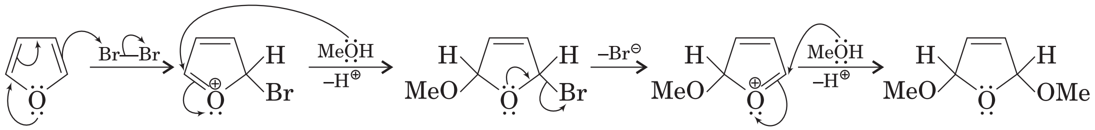

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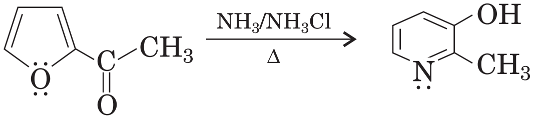

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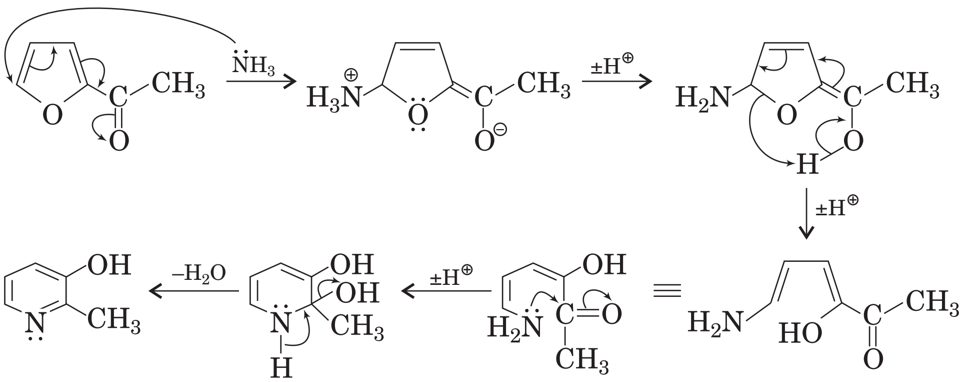
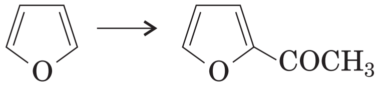
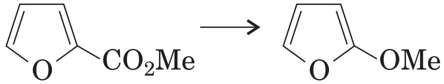


4. How would you carry out the following transformations?

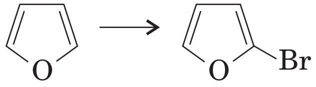
(a)



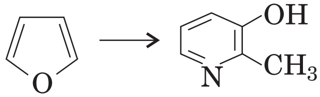
(b)



(c)

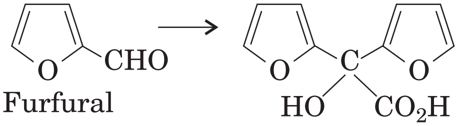


(d)



[C.U. 2011]

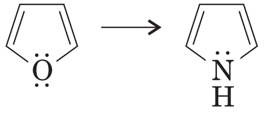
(e)



Furfural

Furilic acid

(f)



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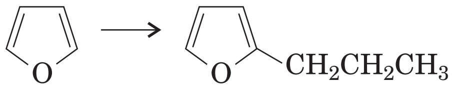
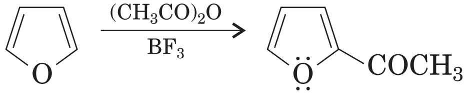
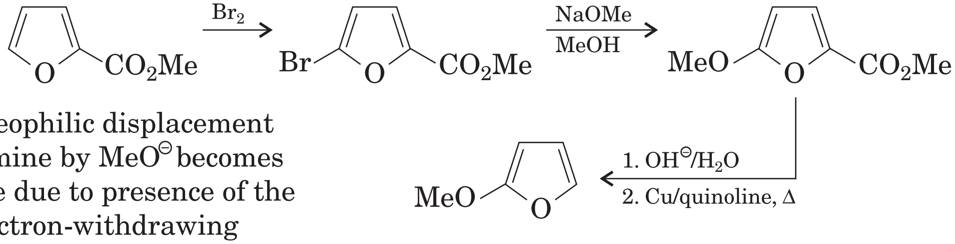


Solution

(a)

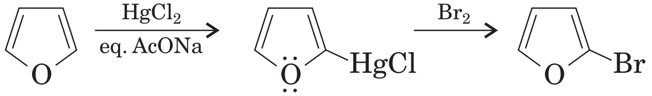


(b)



[Nucleophilic displacement of bromine by MeO$^{\ominus}$ becomes possible due to presence of the electron-withdrawing —CO_2Me group]

(c)



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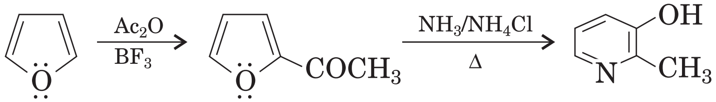

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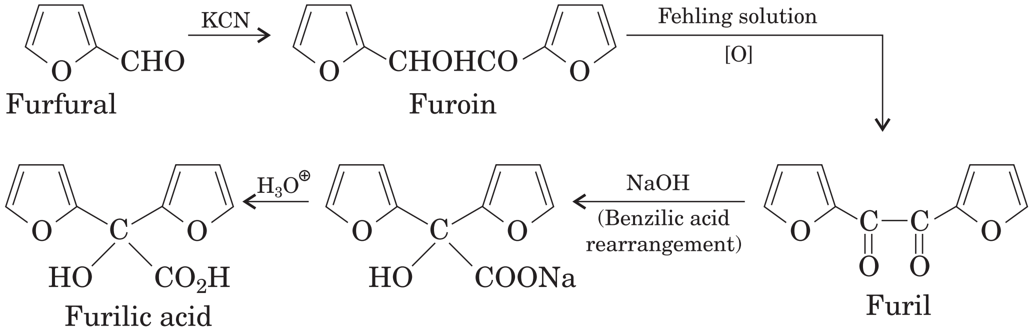

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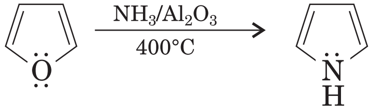

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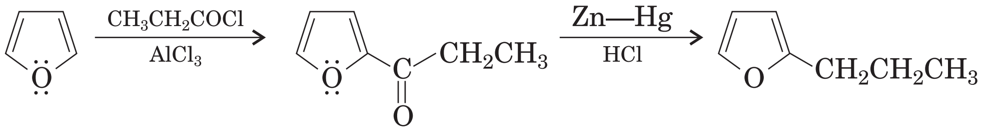
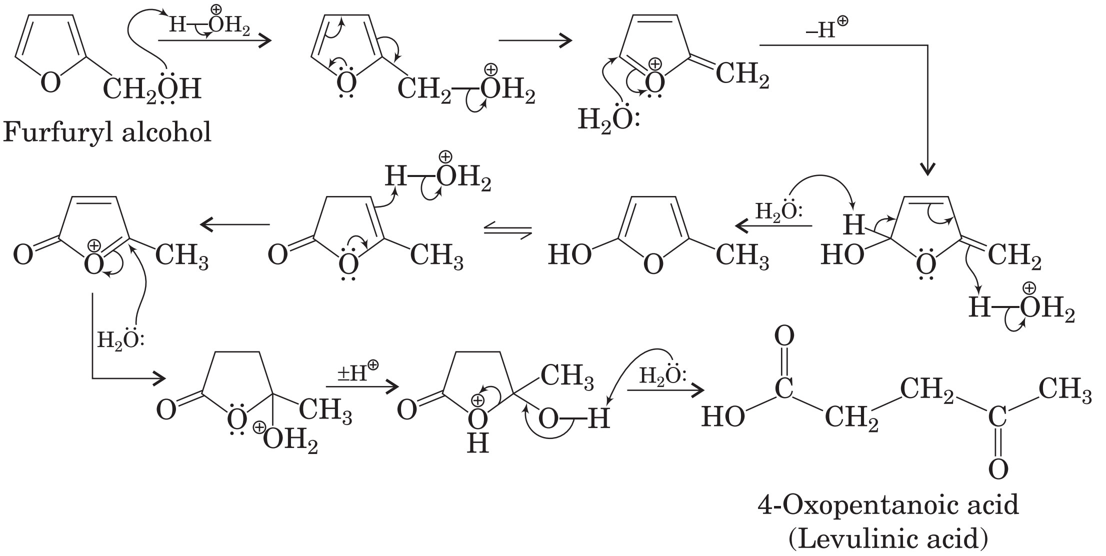


5. What happens when furfuryl alcohol is treated with large excess of dilute hydrochloric acid? Give the mechanism of the reaction involved.

[C.U. 2010]

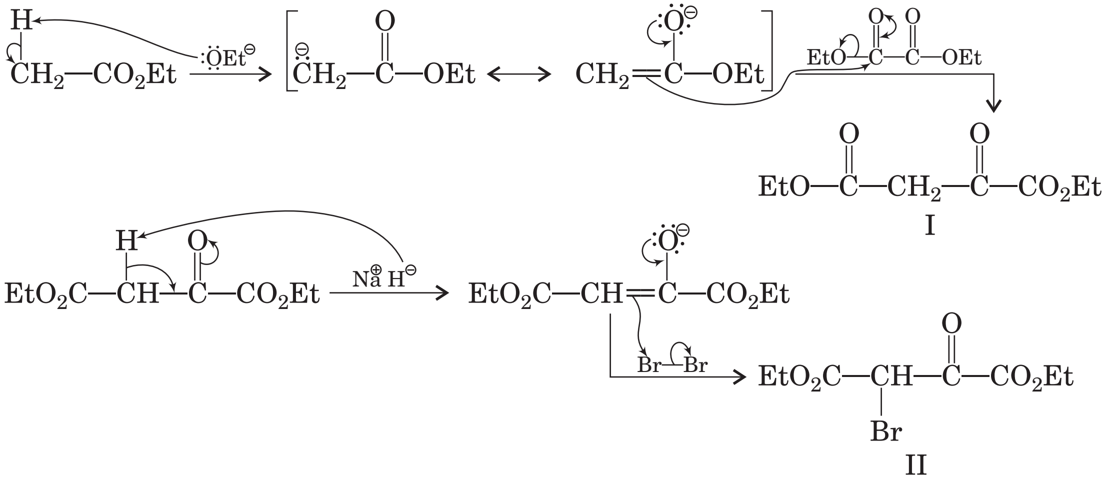
Solution When furfuryl alcohol is treated with large excess of dil. HCl, 4-oxopentanoic acid (levulinic acid) is obtained. The reaction proceeds through the steps as follows:



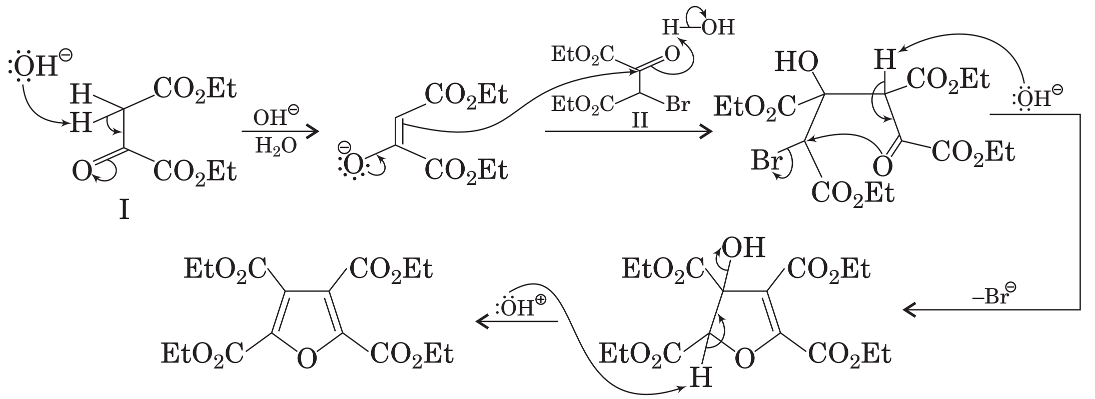
6. **How would you proceed to synthesize ethyl furantetracarboxylate by using ethyl acetate and diethyl oxalate?**

Solution

The Feist-Benary synthesis of the given compound may be carried out as follows:

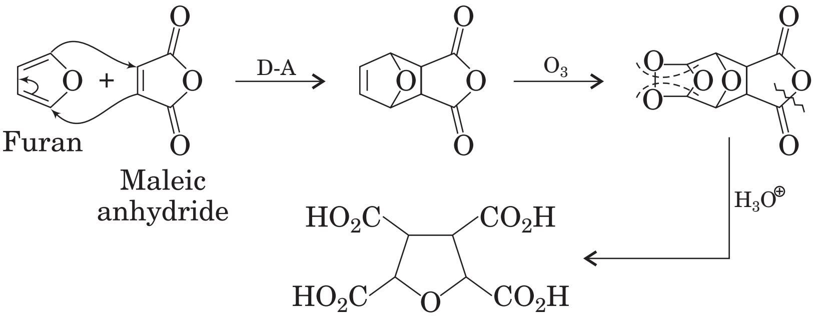


I is then allowed to react with II in the presence of NaOH (or pyridine).



7. How would you prepare tetrahydrofuran-2,3,4,5,-tetracarboxylic acid from furan?

Solution



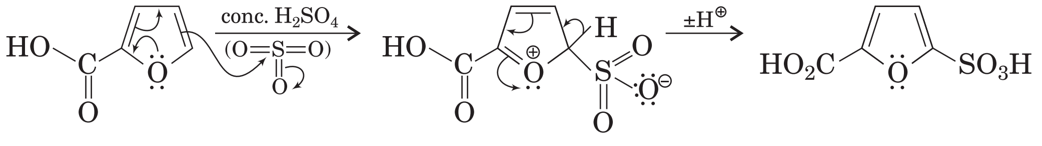
Tetrahydrofuran-2,3,4,5-
tetracarboxylic acid

When the ozonide is treated with dilute acid, it undergoes decomposition to give a dialdehyde which is subsequently oxidized to the corresponding diacid by H_2O_2. The anhydride is also hydrolyzed to give two —COOH groups.

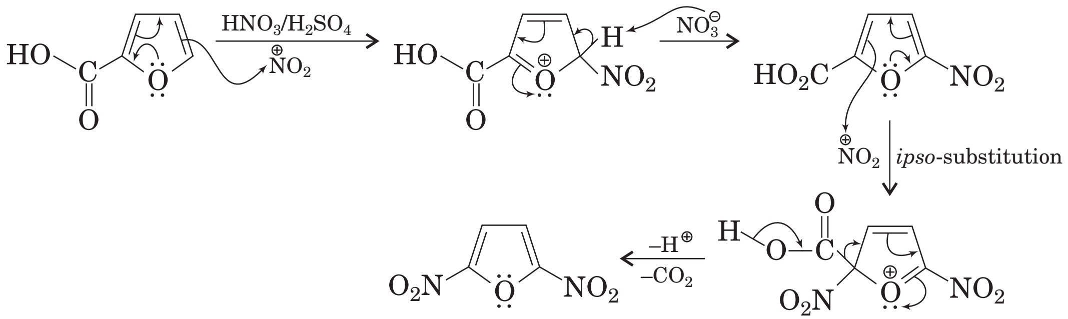
8. Unlike furan, furoic acid can be directly sulphonated with conc. H_2SO_4, and nitrated directly with HNO_3/H_2SO_4. Give reasons and outline the mechanisms of the reactions involved.

Solution Due to presence of the –I group (—COOH) in the ring, polymerization under much acidic conditions does not take place and so, sulphonation and nitration of furoic acid can be carried out directly with conc. H_2SO_4 and HNO_3/H_2SO_4, respectively.

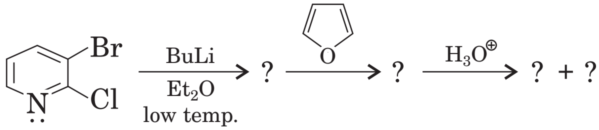
Sulphonation:



Nitration:

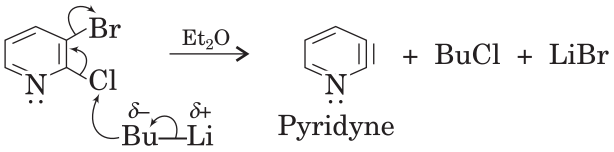


9. Predict the product(s) expected to be formed in each step of the following reaction sequence and give the mechanism involved:

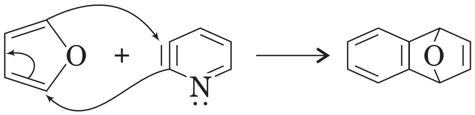


Solution

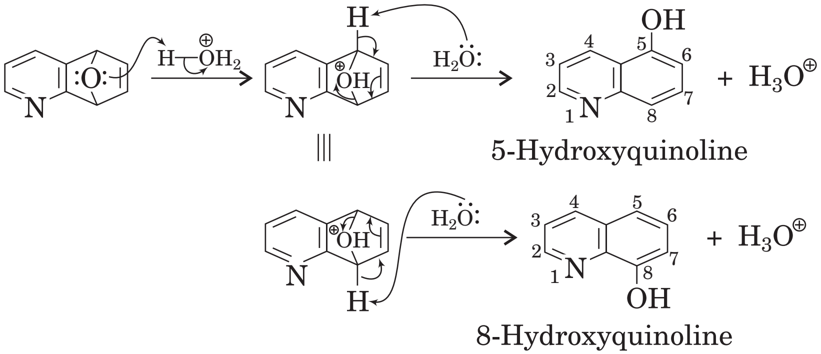
Step 1: When 3-bromo-2-chloropyridine is treated with the base BuLi, pyridyne is obtained.



Step 2: A Diels-Alder reaction between pyridyne and furan to give an adduct.



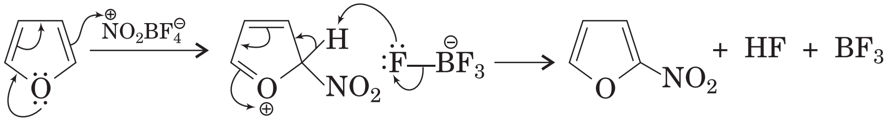
Step 3: Hydrolysis of the adduct to give two isomeric hydroxy quinolines.



10. Furan reacts differently with nitronium fluoroborate and acetylnitrate (in pyridine) to yield 2-nitrofuran. Explain this observation.

[C.U. 2011, 2015]

Solution Furan reacts with nitronium fluoroborate by S_E2 aromatic mechanism to yield 2-nitrofuran as follows:


$\overset{\oplus}{N}O_2BF_4^{\ominus}$
H
:F̈—$\overset{\ominus}{B}F_3$
O
NO_2
O
NO_2
+ HF + BF_3

For the reaction of furan with acetylnitrate in pyridine, see **article no. 6.2.2.2**.

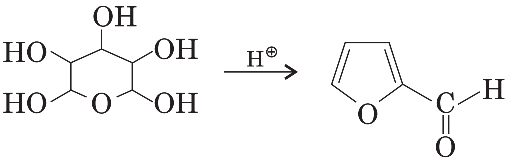
11. $\mathbf{A \xrightarrow{OH^{\ominus}} CH_3COCH_2CO_2Et + ClCH_2COCH_3 \xrightarrow{NH_3} B}$ **[C.U. 2013]**

Identify the products (A and B) and suggest plausible mechanisms for the reactions.

[**Hint:** See **article no. 6.2.2.1** (Feist-Benary synthesis) and **article no. 6.2.1.1** (Hantsch synthesis).]

STUDY PROBLEMS

1. When the following aldopentose (pyranose form) is treated with acid, furfural is obtained. Suggest a reasonable mechanism for this transformation.

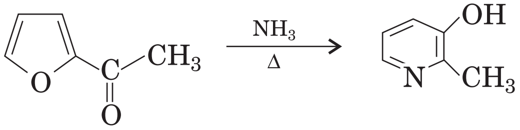


Furfural

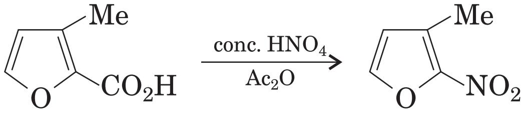
2. How can you obtain pyrrole from furan? Propose the mechanism of the reaction.
[**Hint:** When furan is treated with ammonia in the presence of Al_2O_3 and steam, pyrrole is formed.]

3. Give mechanisms of the following transformations:

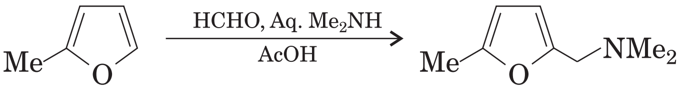
(a)



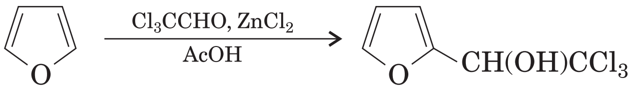
(b)



(c)

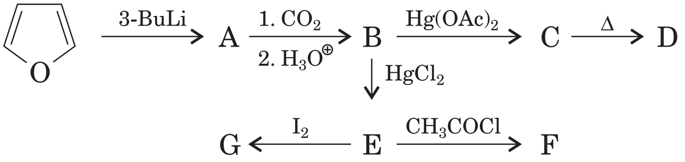


(d)



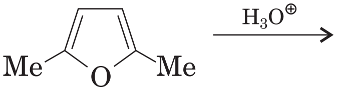
4. Write structures for the products obtained when 2-lithiofuran is allowed to react with (i) cyclohexanone (ii) $Br(CH_2)_7Cl$.

5. Give structures for compounds A – G:



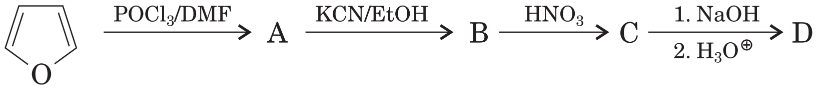
6. Do 2-hydroxyfuran exist? Give your reasoning.
[**Hint:** No. It exists as its two keto tautomers.]

7. Give the steps for the formation of the open-chain compound from the following reaction of 2,5-dimethylfuran:

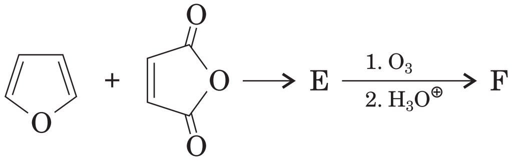


8. Identify the products A – I:

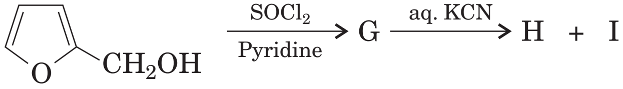
(a)



(b)



(c)



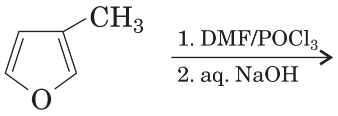
9. Predict the structure of the furan obtained in each of the following syntheses:

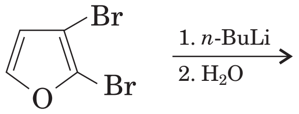
(a) $CH_2{=}CHCH_2MgBr \xrightarrow[\substack{\text{2. } m\text{-CPBA} \\ \text{3. } CrO_3/\text{Pyridine} \\ \text{4. } BF_3}]{\text{1. EtCHO}}$

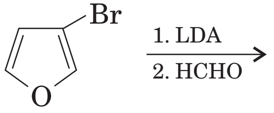
(b) $CH_2{=}C(Me)CH_2MgCl \xrightarrow[\substack{\text{2. } m\text{-CPBA} \\ \text{3. } H_3O^{\oplus}}]{\text{1. } HC(OEt)_3}$

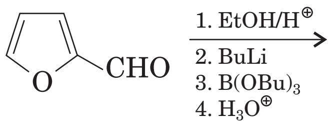
(c) $(MeO)_2CH\ CH_2COMe + ClCH_2CO_2Me \xrightarrow[\text{2. } \Delta]{\text{1. NaOMe}}$

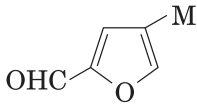
10. Predict structures for the product (major) from the following combinations:

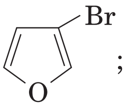
(a) 

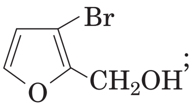
(b) 

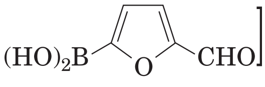
(c) 

(d) 

[**Hint:** (a) 

; (b) 

; (c) 

; (d) 

]

11. Which one is the most common method for the ring synthesis of furans? Write down the mechanism for this ring closing process.

12. With what type of dienophile do furans react most readily and why?

[**Hint:** Due to the aromatic character of furan ring and the inherent strain in the adduct, the cycloadduct is sensitive thermally towards reverting to the starting materials. Because of this, a powerful dienophile like maleic anhydride, DMAD or maleimide is to be used. Furans react with these dienophiles readily to give a good yield of the adduct.]

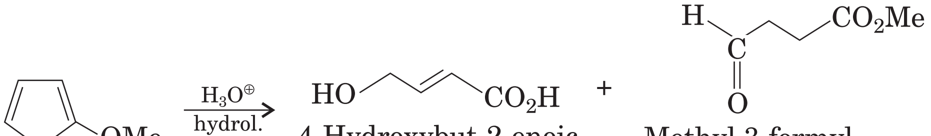
13. Mention three distinctly different reactions of furans which confirm the relatively smaller aromatic resonance stabilization of furan compared to pyrrole and thiophene.

14. Carry out the synthesis of 2-methoxyfuran from methyl α-furoate and any other needed reagents.

15. How can furfural be converted to (a) ethyl 5-bromo-2-furoate and (b) 1,2,5-tribromopentane.

[**Hint:** (a) 1. $Ag(NH_3)_2^{\oplus}$; 2. $EtOH/H^{\oplus}$; 3. Br_2 (b) 1. H_2/Ni ; 2. HBr]

16. Explain the following observation with plausible mechanism:



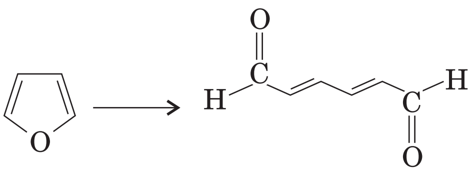
2-Methoxyfuran

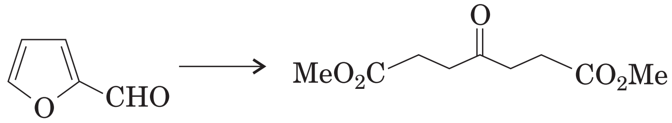
4-Hydroxybut-2-enoic acid

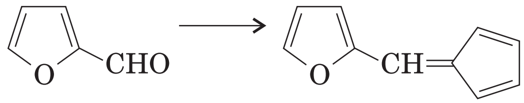
Methyl 3-formylpropanoate

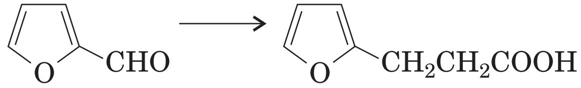
[**Hint:** The 2-protonated 2-methoxyfuran produces the acid and the 3-protonated furan produces the ester.]

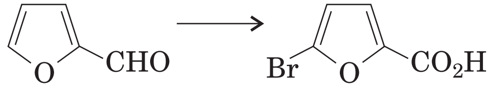
17. How would you carry out the following transformations:

(a) 

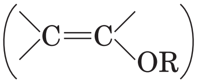
(b) 

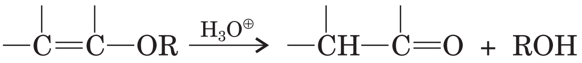
(c) 

(d) 

(e) 

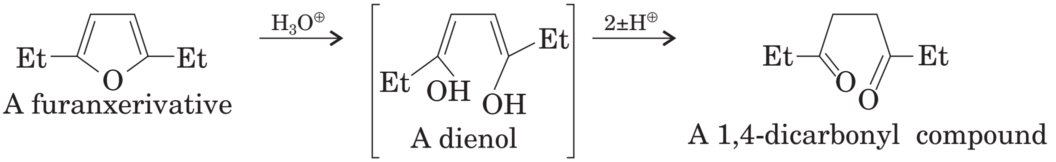
18. Furan behaves as an enol ether. Comment. **[C.U. 2012]**

[**Hint:** Enol ethers, for example, vinyl ethers  undergoes acid-catalyzed hydrolysis to yield an alcohol ROH) and a carbonyl compound of the corresponding enol tautomer.



$$-\overset{|}{C}=\overset{|}{C}-OR \xrightarrow{H_3O^{\oplus}} -\overset{|}{C}H-\overset{|}{C}=O + ROH$$

Similarly, furans, which are expected to be an enol ether obtained from the enol tautomer of a 1,4-dicarbonyl compound, undergoes acid-catalyzed hydrolysis to yield the 1,4-dicarbonyl compound through a dienol. For example:



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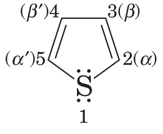
6.2.3 Thiophene and Its Derivatives

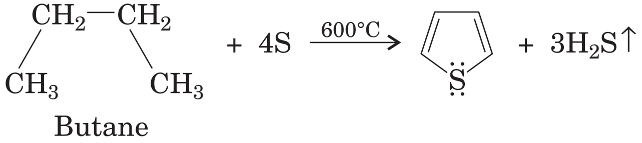
Thiophene is the sulphur analog of furan and occurs naturally in the benzene fraction of coal tar and also, in crude petroleum. Since the boiling point of thiophene (84°C) is close to benzene (80°C), it is not possible to separate these two compounds by fractional distillation. A large number of thiophene derivatives occur in plants and animal metabolism. Biotin, one of the vitamins, is a tetrahydrothiophene. Banmonth (Pyrantel), a valuable anthelminth used in animal husbandry, is one of the few thiophene compounds in chemotherapy. Contribution of two electrons by the sulphur atom completes the aromatic sextet in the molecule of thiophene and as sulphur is less electronegative than oxygen or nitrogen, it is more aromatic than other five-membered heterocycles. Like pyrrole and furan, the heteroatom of thiophene is also numbered 1.

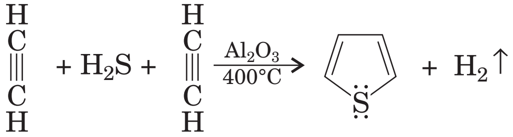


Thiophene

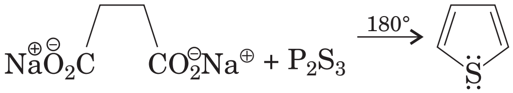
6.2.3.1 Synthetic Methods

1. From butane and acetylene Thiophene is manufactured (i) by cyclization of butane with sulphur and (ii) by passing a mixture of acetylene and hydrogen sulphide over heated alumina (Al_2O_3).

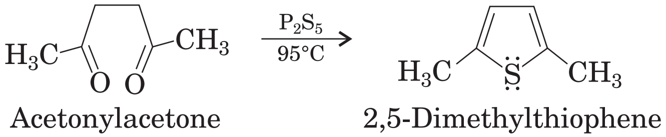




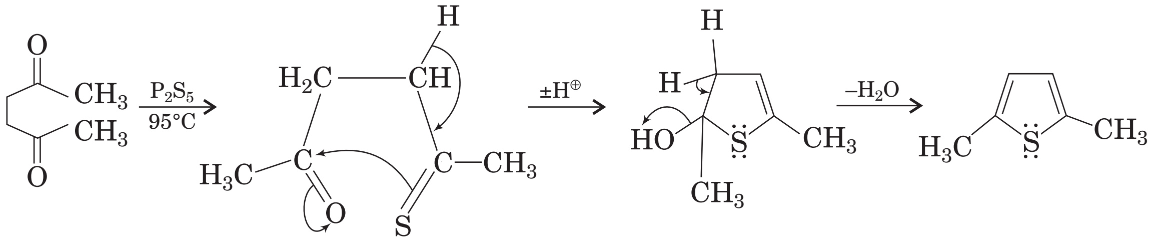
2. From sodium succinate The laboratory method for preparing thiophene consists of heating a mixture of sodium succinate and phosphorus trisulphide (P_2S_3).


$Na^{\oplus}\overset{\ominus}{O_2}C$
$CO_2^{\ominus}Na^{\oplus}$ + P_2S_3
180°
S

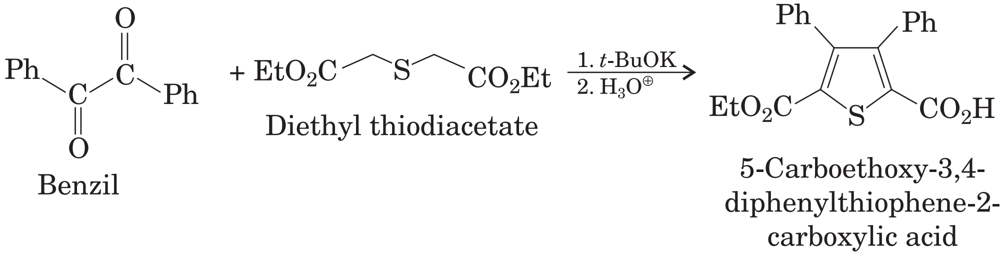
3. Paal–Knorr synthesis This is the most general method for the synthesis of substituted thiophenes. It involves heating an enolizable 1,4-dicarbonyl compound with phosphorus pentasulphide (P_2S_5) which acts as the source of sulphur. For example, when acetonylacetone is heated with P_2S_5, 2,5-dimethylthiophene is obtained.



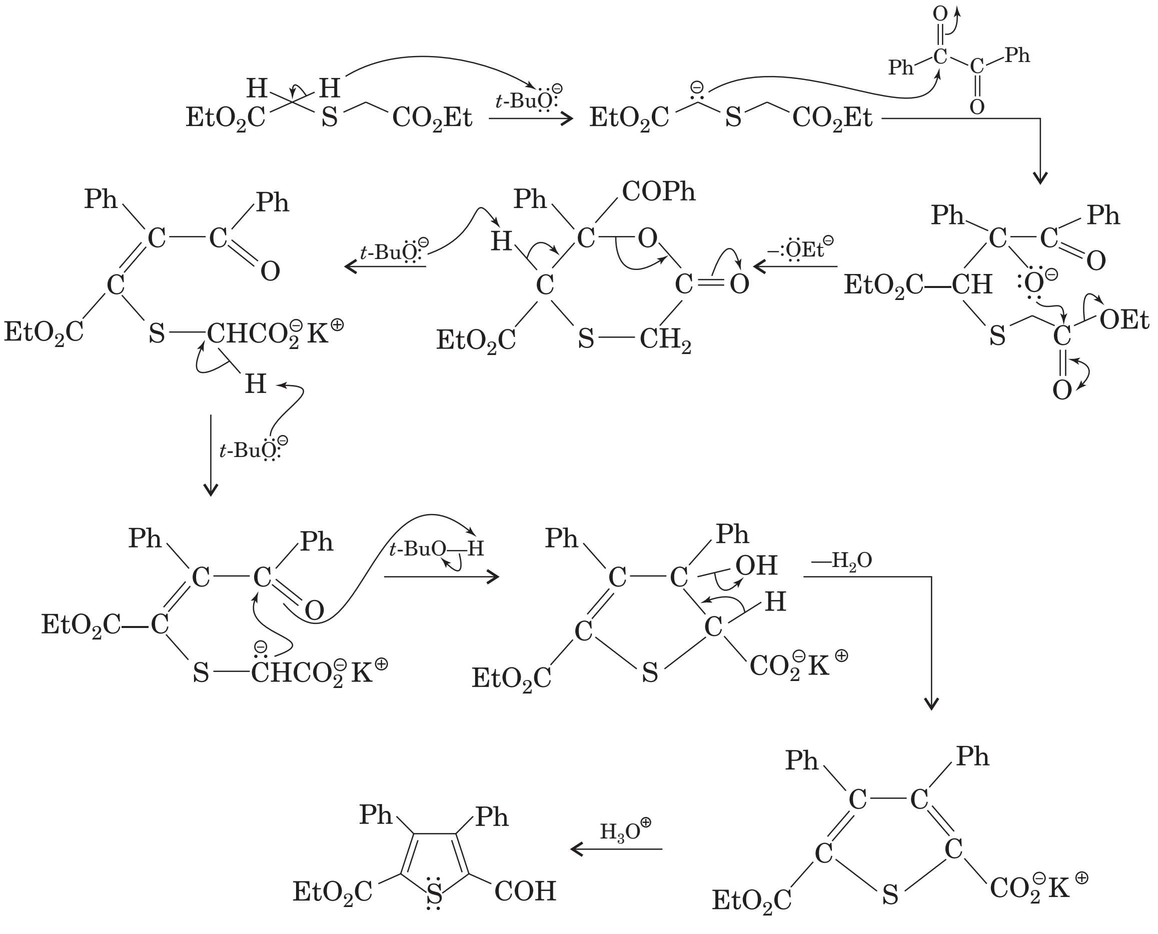
Mechanism of the reaction The reaction proceeds through the steps as follows. In the first step a C═O group is converted to a C═S group and in the second step, cyclization involving nucleophilic attack by the more polarizable sulphur on carbonyl carbon followed by dehydration occurs to give the product.



4. Hinsberg synthesis This method involves the reaction between a 1,2-dicarbonyl compound and diethyl thiodiacetate in the presence of a strong base. For example, when benzil is treated with diethyl thiodiacetate in the presence of *t*-BuOK, and finally acidified, 5-carboethoxy-3,4-diphenylthiophene-2- carboxylic acid is obtained.



Mechanism of the reaction The mechanism of the reaction involves two consecutive aldol reactions between the reactants. This can be outlined as follows:

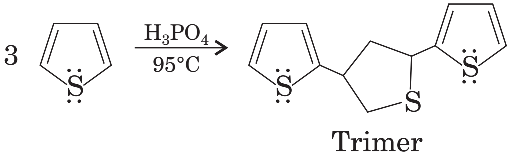


6.2.3.2 Properties and Reactions

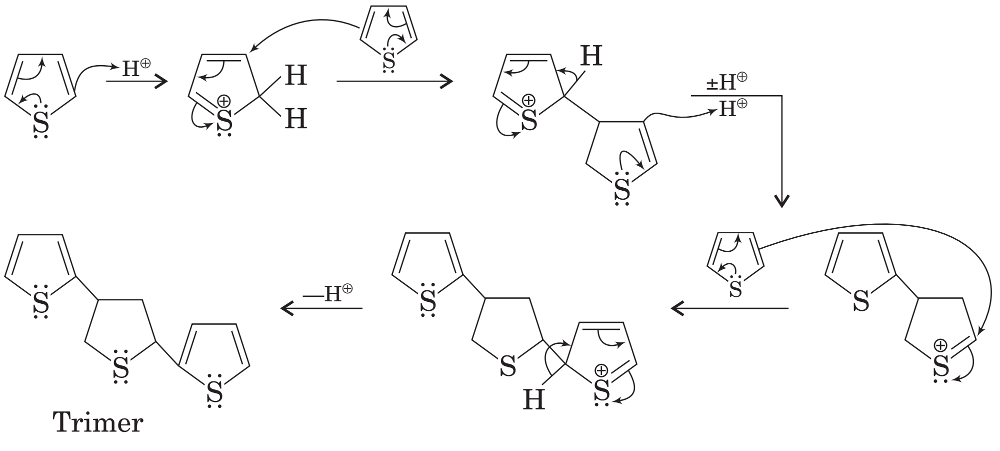
Thiophene is a colourless liquid. It has a benzene-like smell and is immiscible with water but soluble in most organic solvents. The magnitude of resonance energy of thiophene is higher than that of pyrrole and furan. Therefore, it is most aromatic and least reactive among the three five-membered heterocycles. Since the sulphur atom belongs to the second row elements of the periodic table, it can expand its valence shell by using the empty *d*-orbitals in hybridization. Consequently, instead of having six electrons in five orbitals (as in the case of pyrrole and furan) thiophene by using *d*-orbital might have six electrons in six orbitals. This fact probably accounts for the very much stability of thiophene and its resemblance to benzene in physical and chemical properties.

Some important reactions of thiophene are as follows:

1. Reactions of protonated thiophenes When thiophene is treated with hot phosphoric acid, a trimer is obtained.

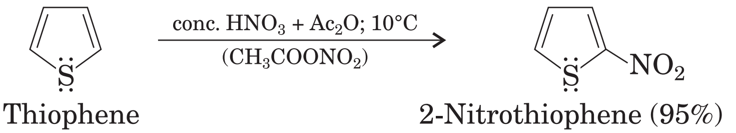


Mechanism of the reaction:



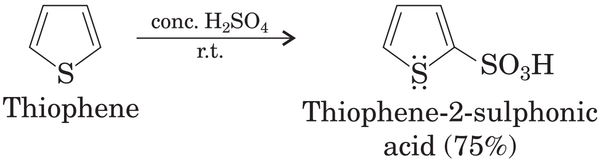
2. Electrophilic substitutions The order of reactivity towards electrophilic substitutions at carbon amongst the five-membered heterocycles is pyrrole > furan > thiophene. Thus, thiophene is least reactive, yet it is much more reactive than benzene by a factor of 10^3–10^5. The majority of the reactions follow the same mechanistic pathway as those of benzene and the preferential attack by the electrophile takes place at position-2.

(i) Nitration Nitration of thiophene is carried out with the mild nitrating agent acetyl nitrate CH_3COONO_2 (a mixture of acetic anhydride and nitric acid) at 10°C to yield 2-nitrothiophene as the major product (95%).



The mechanism of the reaction is similar to that of furan. When nitration is carried out with nitration mixture (conc. HNO_3 + conc. H_2SO_4), 3-nitrothiophene is obtained in 15% yield along with 85% of 2-nitrothiophene. Nitration of 2-halogen substituted thiophene with HNO_3/H_2SO_4 gives exclusively the 4-nitro product. Nitration of thiophene-2-carboxylic acid with HNO_3/H_2SO_4 gives a mixture of 5-nitro (75%) and 4-nitro (25%) products.

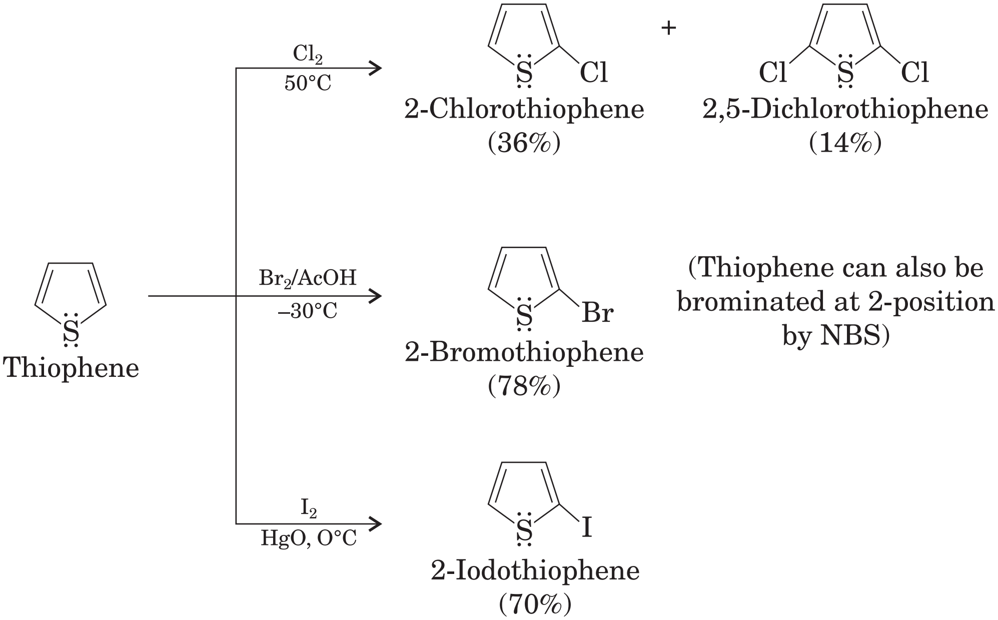
(ii) Sulphonation In contrast to benzenes, it undergoes ready sulphonation by concentrated sulphuric acid at room temperature.



Much better yield (90%) of thiophene-2-sulphonic acid is obtained when sulphonation is carried out with pyridine-SO_3.

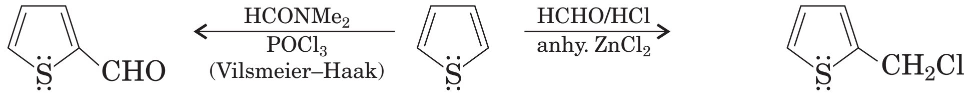
The mechanism of sulphonation with conc. H_2SO_4 is similar to that of benzene.

(iii) Halogenation:



(Thiophene can also be brominated at 2-position by NBS)

(iv) Chloromethylation and formylation Thiophene can be chloromethylated by formaldehyde and hydrogen chloride in the presence of anhydrous zinc chloride. This can be formylated by the Vilsmeier–Haak reaction.

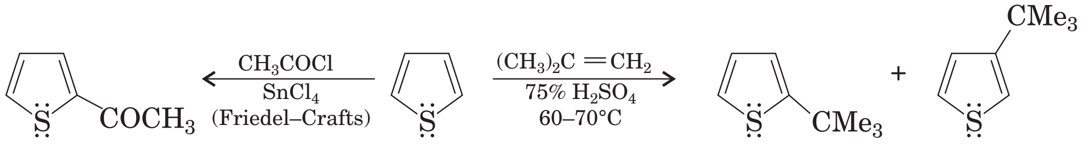


Thiophene-2-carbaldehyde

2-Chloromethylthiophene

Thiophene-2-carbaldehyde undergoes the Cannizzaro reaction and the benzoin condensation.

(v) Alkylation and acylation:

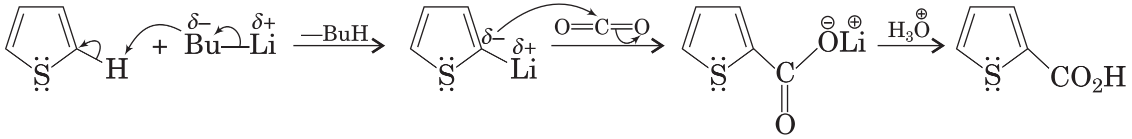


2-Acetylthiophene

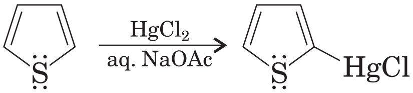
2-*tert*-Butylthiophene

3-*tert*-Butylthiophene

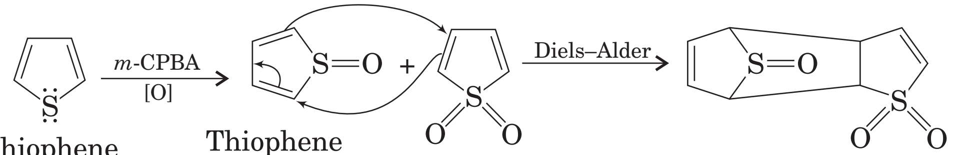
3. Metallation of thiophene Thiophene reacts with butyllithium to form 2-thienyllithium which can be converted to thiophene-2-carboxylic acid.



Thiophene can be mercurated at the 2-position by treating with mercuric chloride in aqueous sodium acetate.



4. Oxidation Thiophene on oxidation with *m*-CPBA gives a mixture of sulfoxide and sulphone. Both of them are unstable and react instantly to give a Diels–Alder adduct.



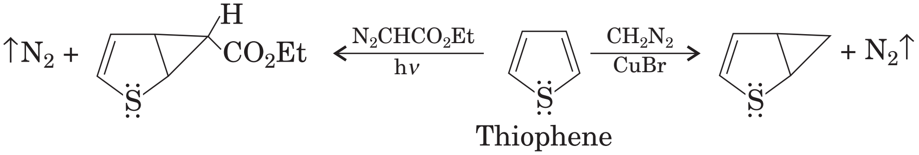
Thiophene

Thiophene sulfoxide

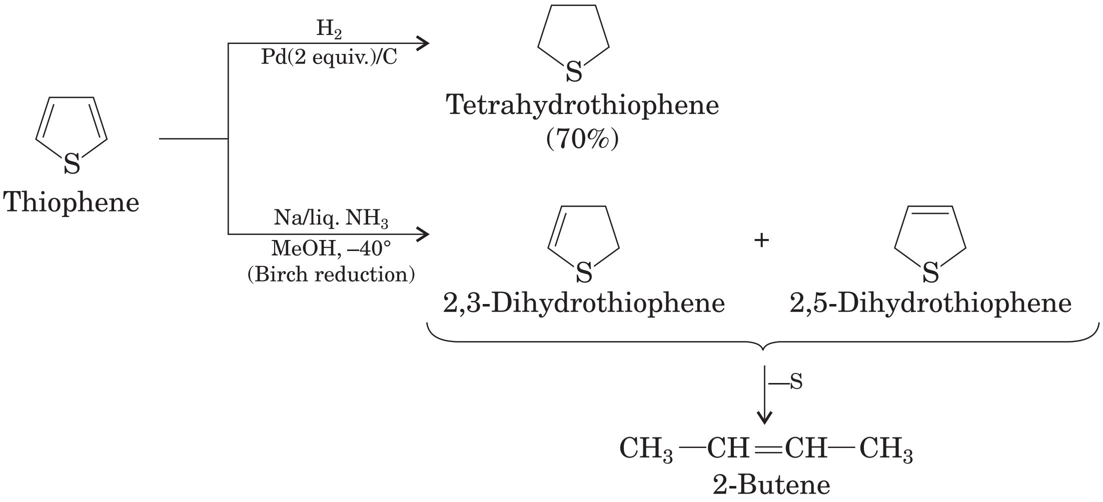
Thiophene sulfone

Adduct

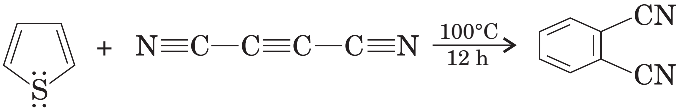
5. Reaction with carbenes Carbenes (generated *in situ*) add on to the C-2—C-3 bond of thiophene to give the cyclopropane derivative.



6. Reduction Thiophene or reduction give products depending on the reducing agent and the reaction conditions.

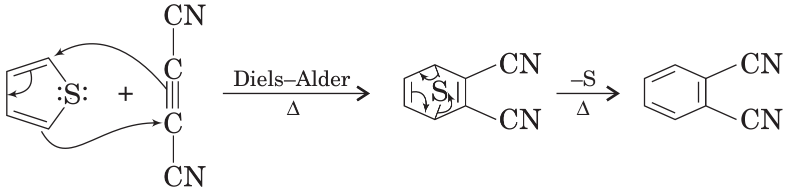


7. Diels–Alder reaction Thiophene generally refuses to undergo the Diels–Alder reaction. However, it combines with the extremely reactive dienophile dicyanoacetylene.



Mechanism of the reaction

The initially formed Diels–Alder adduct undergoes cheletropic reaction to yield 1,2-dicyanobenzene.

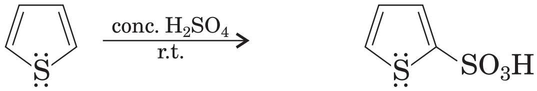


SOLVED PROBLEMS

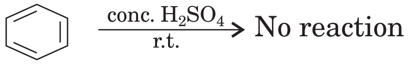
1. Why is commercial benzene normally contaminated with thiophene? How can thiophene-free benzene be prepared from contaminated benzene?

Solution Thiophene occurs naturally in the benzene fraction of coaltar. Since the boiling points of benzene (80°C) and thiophene (84°C) are very close, it is not possible to separate these two compounds completely by fractional distillation. Because of this, commercial benzene is normally contaminated with thiophene.

Thiophene can be separated from benzene by making use of the ability of thiophene to undergo sulphonation reaction more readily than benzene. The resonance hybrid of thiophene shows that the ring carbons are more electron dense than those of benzene. For this reason, thiophene undergoes sulphonation at a faster rate than benzene. In fact, sulphonation of thiophene can be carried out by conc. H_2SO_4 at room temperature, whereas sulphonation of benzene cannot be carried out at room temperature. The technical grade benzene is shaken repeatedly with about 15% of its volume of cold conc. H_2SO_4 until the acid layer is colourless or very pale yellow. Thiophene undergoes sulphonation readily and the resulting thiophene-2-sulphonic acid dissolves in the acid layer. The benzene layer is separated, washed with water, dried with fused $CaCl_2$ and finally distilled.



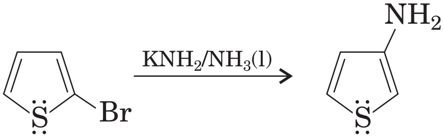
Thiophene Thiophene-2-sulphonic acid (water-soluble)



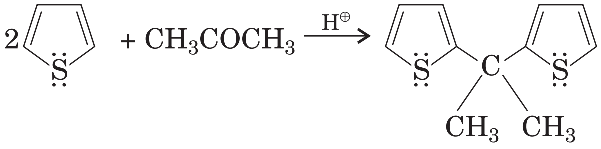
Benzene

2. Suggest a mechanism for each of the following reactions:

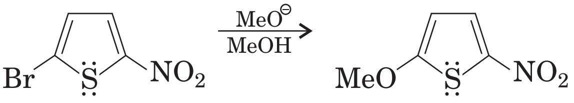
(a)



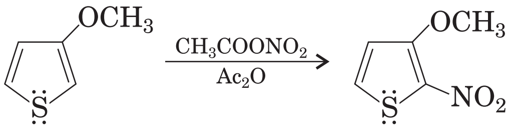
(b)



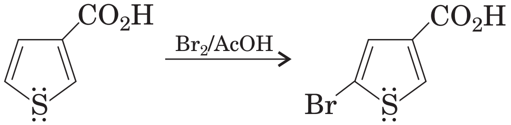
(c)



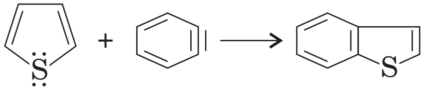
(d)



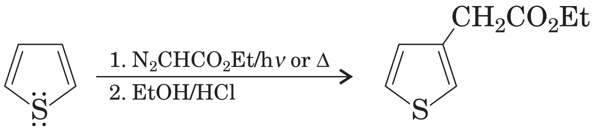
(e)



(f)

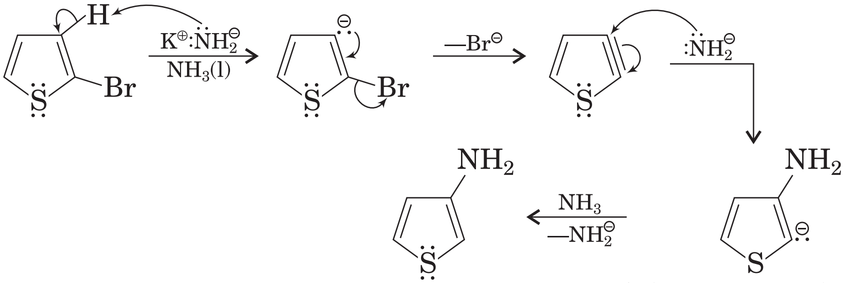


(g)



Solution

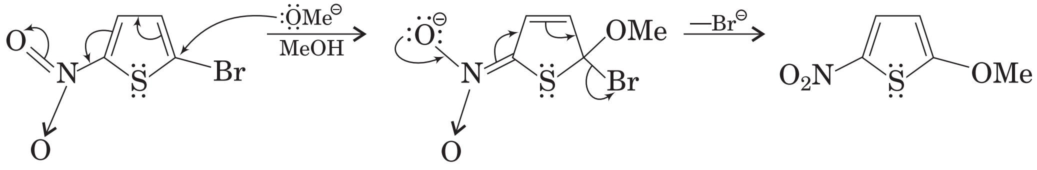
(a)



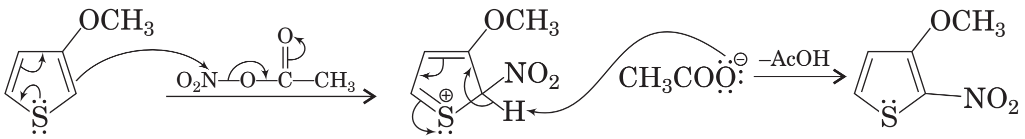
(The negative charge adjacent to sulphur is stable)

(b) See the answer to the **Solved Problem 3(i)** of **article 6.2.2**.

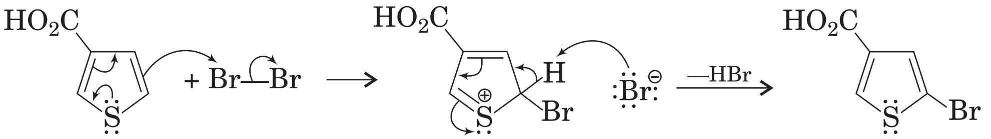
(c) The compound undergoes nucleophilic substitution of bromine due to presence of the electron-withdrawing —NO_2 group which is properly placed to stabilize a negative charge.



(d) 3-Methoxythiophene on nitration yields 2-nitro-3-methoxythiophene because the —OCH_3 group is electron-donating and *ortho*-directing.



(e) Electrophilic attack by $Br^{\oplus}$ avoids placing the +ve charge on C-3, which is already attached to an electron withdrawing —COOH group. Substitution actually takes place at the position *meta* to the —COOH group, i.e., at C-5.



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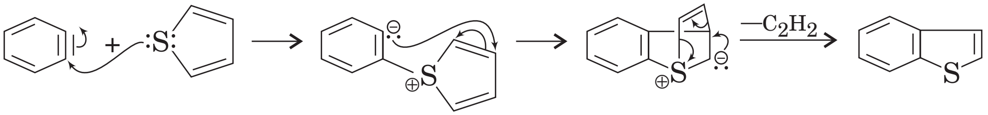

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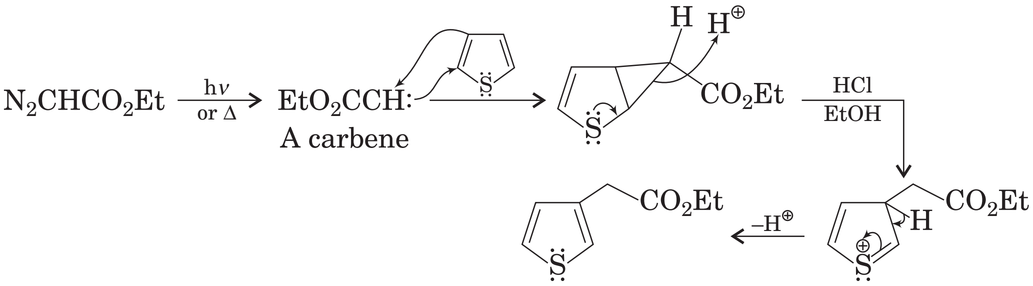
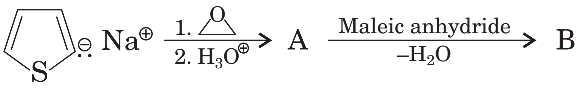
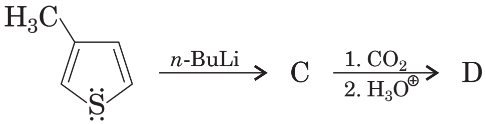


3. Provide structures for compounds A–K in the following reaction sequences:

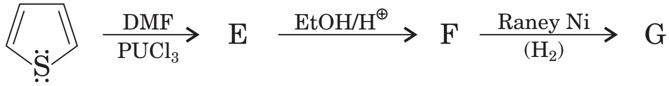
(a)



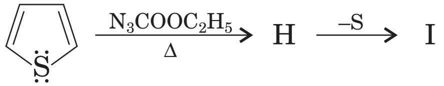
(b)



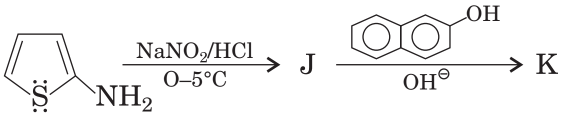
(c)



(d)

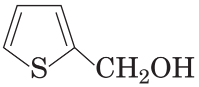


(e)

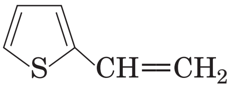


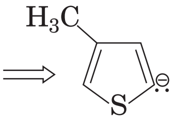
Solution

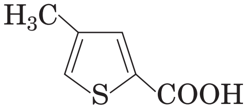
(a) A ⟹

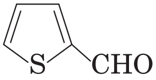


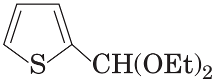
; B ⟹



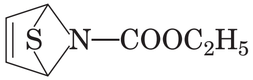
(b) C ⟹ 

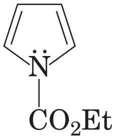
; D ⟹ 

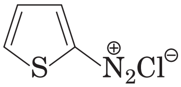
(c) E ⟹ 

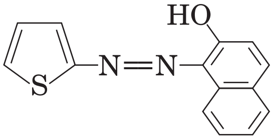
; F ⟹ 

; G ⟹ $CH_3(CH_2)_3CH(OEt)_2$

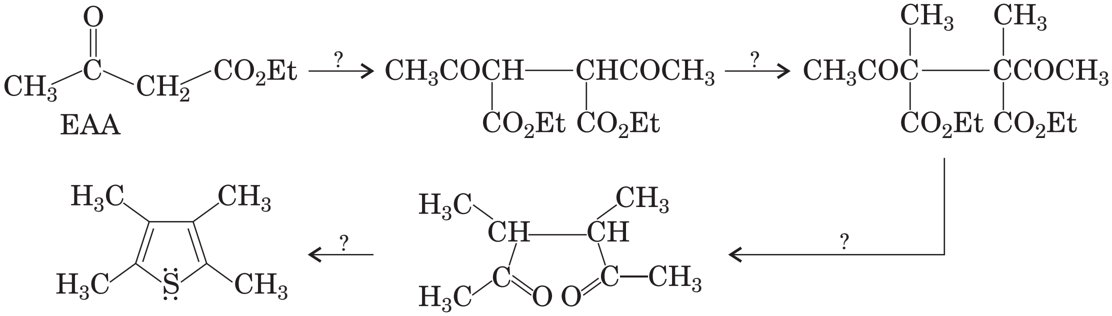
(d) H ⟹ 

; I ⟹ 

(e) J ⟹ 

; K ⟹ 

4. **Identify the reagent(s) required in each step of the following reaction sequence leading to the formation of 2,3,4,5-tetramethylthiophene:**



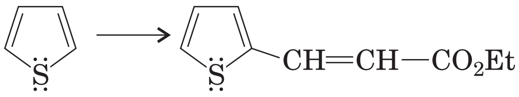
Solution **Step 1:** 1. NaOEt ; 2. I_2 ; **Step 2:** 1. NaOEt (2 equiv.) ; 2. CH_3I (2 equiv.) ; **Step 3:** 1. $OH^{\ominus}/H_2O$; 2. $H_3O^{\oplus}/\Delta$; **Step 4:** P_2S_5/Δ.

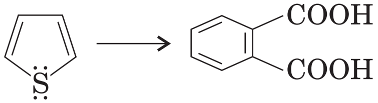
5. **Thiophene undergoes Diels–Alder reaction under specific conditions. Comment on this statement.** **[C.U. 2012]**

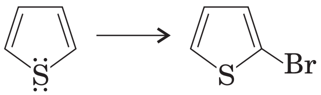
Solution See **article no. 6.2.3.2**.

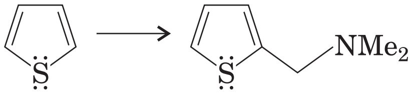
STUDY PROBLEMS

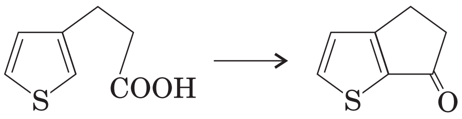
1. How would you carry out the following transformations:

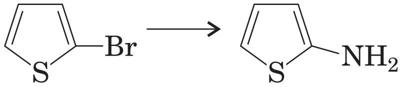
(a) 

(b) 

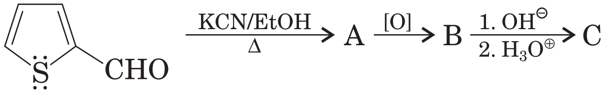
(c) 

(d) 

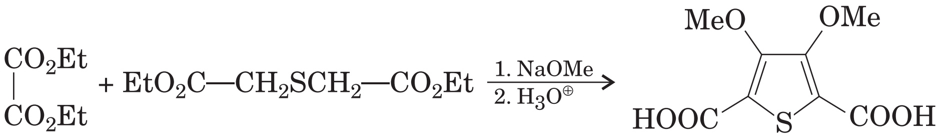
(e) 

(f) 

2. Predict the products (A–C) and suggest a mechanism for step 1 and step 3 of the following reaction sequence:



3. Suggest a reasonable mechanism for the following reaction:

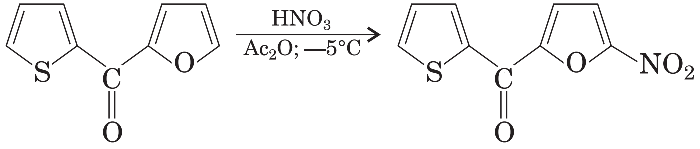


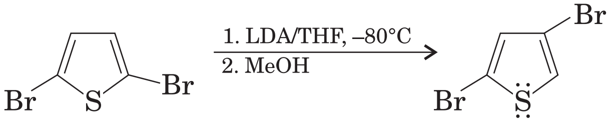
4. List the reactions with suitable examples to demonstrate the similarities between thiophene and benzene.

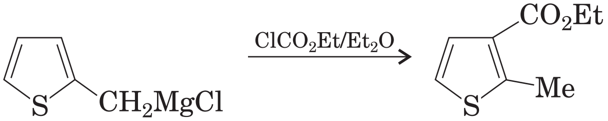
5. How would you prepare *n*-decane from thiophene?

6. How could one transform 2,5-dimethylthiophene into (i) its S-oxide and (ii) S, S-dioxide.

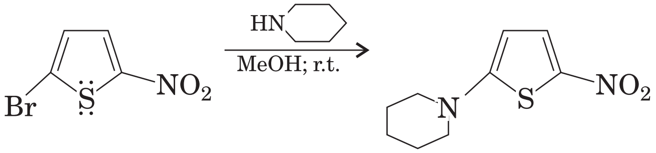
7. Explain the following observations:

(a) 

(b) 

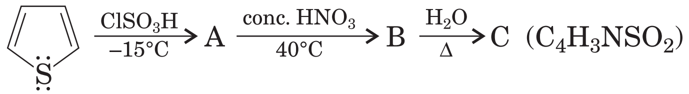
(c) 

(d)



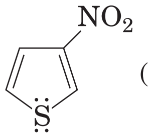
8. Predict the structure of the compounds obtained when thiophene is treated successively with (i) BuLi, (ii) CO_2, (iii) $H_3O^{\oplus}$ and (iv) thiophene in the presence of P_4O_{10}.

9. Identify A, B and C in the following reaction sequence:



Explain why C cannot be synthesized in one step from thiophene.

[**Hint:** C ⟹



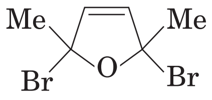
($C_4H_3NSO_2$)]

10. How could one introduce the following substituents at the 2-position of thiophene: (i) —CH, (OH) *t*-Bu, (ii) —Ph and (iii) —CH_2CH_2OH?

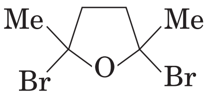
11. Identify A, B, C and D in the following sequence of reactions:

$$\text{2,5-Dimethylfuran} \xrightarrow[\text{MeOH; 0°C}]{Br_2} A \xrightarrow{H_2/Ni} B \xrightarrow{H_3O^{\oplus}} C \xrightarrow[\Delta]{P_2S_5} D$$

[**Hint:** A ⟹

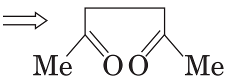


; B ⟹

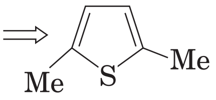


;

C ⟹



; D ⟹



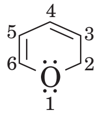
]

12. Discuss a method in which a common precursor can be used to synthesize furan, thiophene and pyrrole.

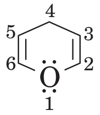
[**Hint:** All the three five-membered heterocyclic compounds can be synthesized from 1,4-dicarbonyl compounds. The method is known as *Paal-Knorr synthesis.*]

6.3 SIX-MEMBERED HETEROCYCLIC COMPOUNDS WITH ONE HETEROATOM

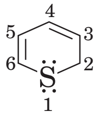
Typical six-membered heterocyclic compounds include α-pyran, γ-pyran, thiopyran and pyridine.



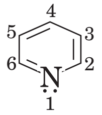
α-Pyran



γ-Pyran



Thiopyran



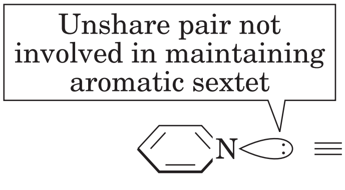
Pyridine

Out of these four compounds, only the chemistry of pyridine is discussed in this article.

6.3.1 Pyridine and Its Derivatives

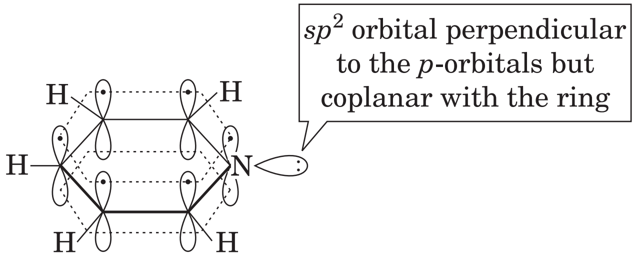
Pyridine is the simplest and probably the best-known heterocyclic compound. It is found in coaltar and bone-oil. It is an important solvent and raw material for the synthesis of a large number of industrially important compounds. It forms the basic skeleton of a number of alkaloids and of many synthetic drugs. It is obtained from light oil fraction of coal-tar by treating the latter with dilute sulphuric acid. This dissolves pyridine and other basic substances. The acid layer is neutralized with NaOH and the liquid is repeatedly fractionated.

Structure of pyridine The structure of pyridine has close resemblance with that of benzene (the nitrogen atom replaces one of the CH units in benzene ring). The five carbon atoms and the nitrogen atom of pyridine are sp^2-hybridized and so, all of them lie in one plane. Nitrogen utilizes two sp^2 orbitals, each containing one electron, to form two N—C σ bonds. The remaining sp^2 orbital carries an unshared pair of electrons. This orbital lies in the plane of the ring, but is directed away from it. The singly-occupied p-orbital on each carbon and the nitrogen atom overlaps each other to form a π-electron cloud of six π-electrons which lies above and below the plane of the ring. The π system of pyridine is isoelectric with the π system of benzene. Like benzene it obeys Huckel's rule and is aromatic. The nonbonding electrons on nitrogen in pyridine are not used to complete the aromatic sextet and therefore, unlike pyrrole, these are readily available for co-ordinating with a proton. This explains why pyridine is more basic than pyrrole.



≡

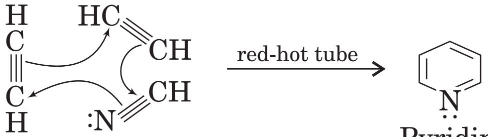
Pyridine
[aromatic: $(4n + 2)$ π electrons, where $n = 1$]


sp^2 orbital perpendicular to the p-orbitals but coplanar with the ring
H
H
H
N
H
H

Orbital picture of pyridine

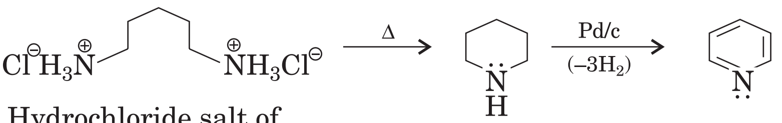
6.3.1.1 Synthetic Methods

1. From acetylene and hydrogen cyanide Pyridine can be synthesized by passing a mixture of acetylene and hydrogen cyanide through a red-hot tube.



Pyridine

2. From the hydrochloride salt of pentamethylenediamine Another method consists in heating the hydrochloride salt of pentamethylenediamine followed by oxidation of the product (piperidine), either with concentrated H_2SO_4 at 300°C, or by dehydrogenation (Pd-C).

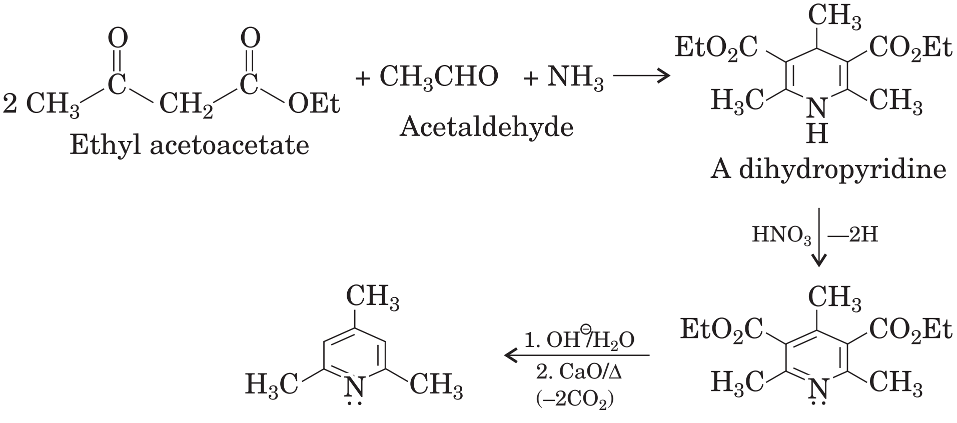


Hydrochloride salt of pentamethylemediamine

Piperidine

Pyridine

3. Hantzsch synthesis This is probably the most important synthesis of pyridine and involves condensation of a *β*-dicarbonyl compound (2 moles) with an aldehyde (1 mole) and ammonia (1 mole). One mole of the *β*-dicarbonyl compound undergoes base-catalyzed condensation with the aldehyde to form an *α*,*β*-unsaturated carbonyl compound. The resulting enone has two carbonyl groups at one end of the double bond and is, therefore, a very good Michael acceptor. A second molecule of enolate does a conjugate addition to complete the carbon skeleton of the molecule. Ammonia then attacks either of the ketones and cyclizes on to the other to form a dihydropyridine. Since ketones are more electrophilic than esters it is to be expected that ammonia will prefer to react there. The dihydropyridine is then oxidized with HNO_3 or DDQ to form the corresponding pyridine.



Ethyl acetoacetate

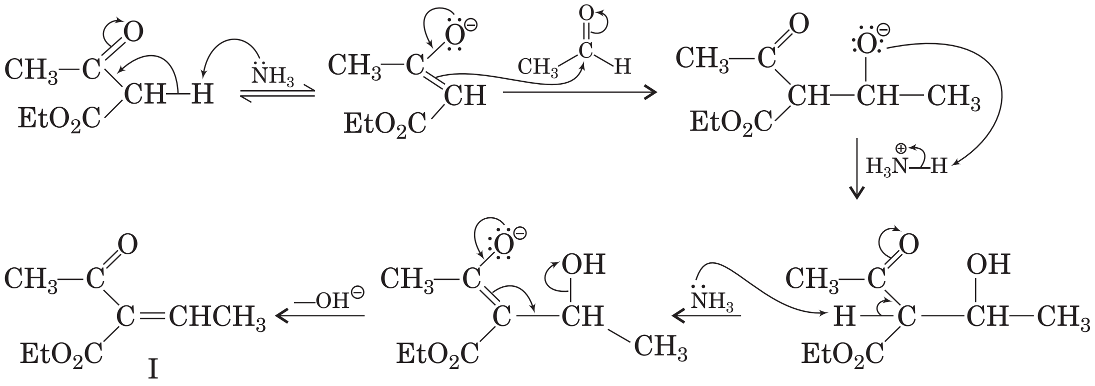
Acetaldehyde

A dihydropyridine

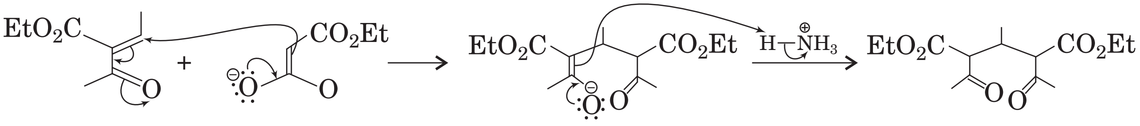
2,4,6-Trimethylpyridine

Mechanism of formation of the dihydropyridine:

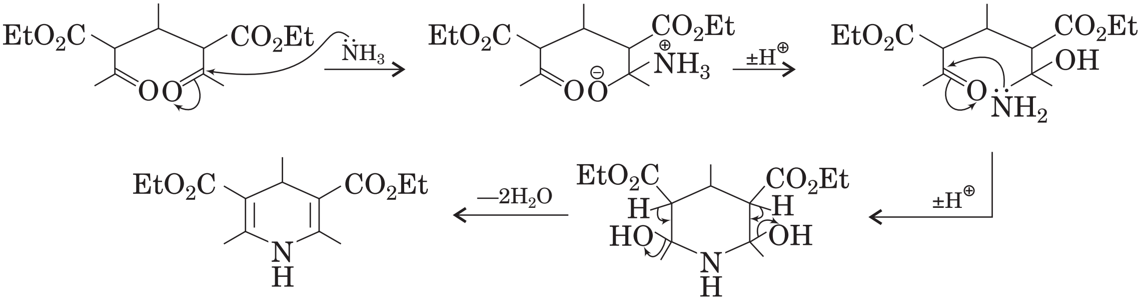
- **Formation of an α, β-unsaturated carbonyl compound (I):**



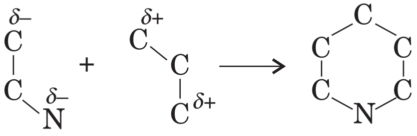
- **Formation of a 1,5-diketone**



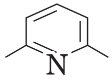
- **Formation of a dihydropyridine**



Hantzsch pyridine synthesis actually involves combination of two aliphatic skeletal fragments such as follows:

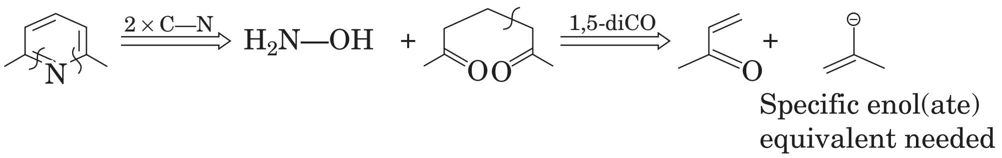


Synthesis of Some Pyridine Derivatives (Target Molecules) through Disconnection Approach

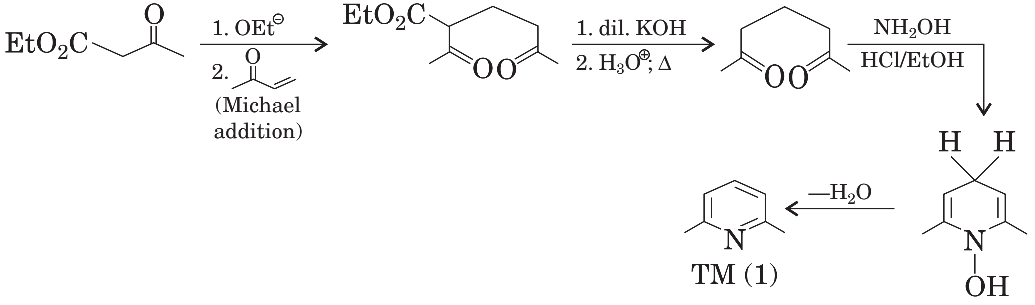
1.  (2,6-Dimethylpyridine)

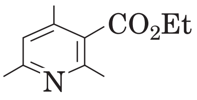
TM(1)

Retrosynthetic analysis



Synthesis

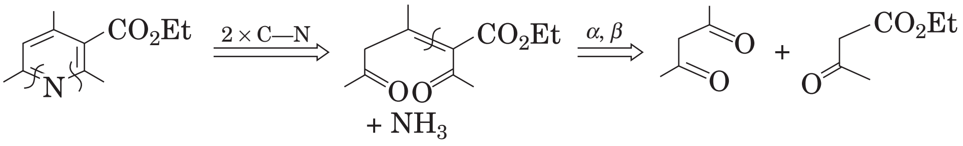


2. 

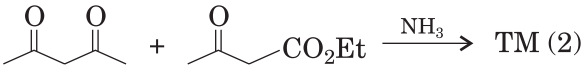
(Ethyl 2,4,6-trimethylpyridine-3-carboxylate)

TM (2)

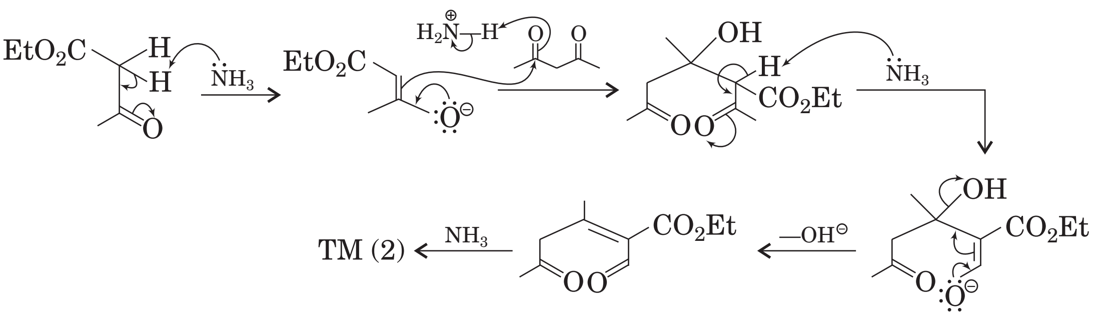
Retrosynthetic analysis



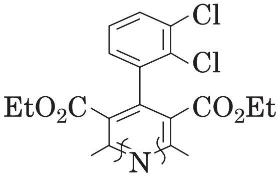
Synthesis



Mechanism

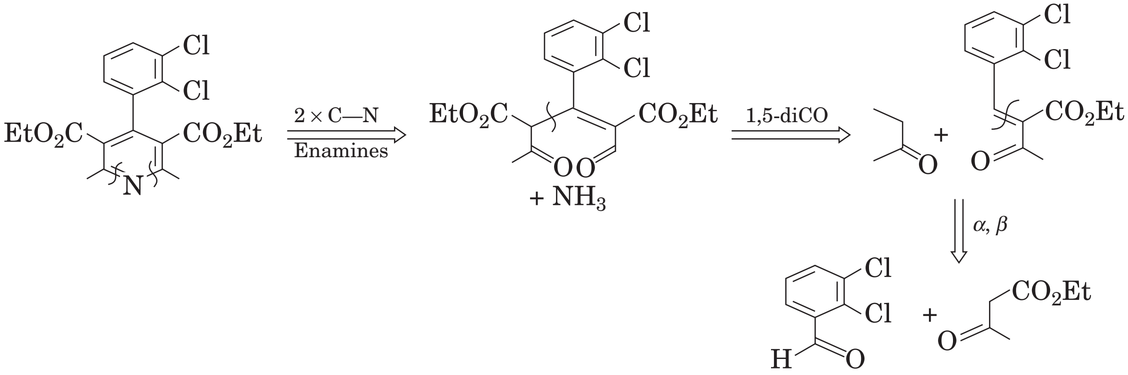


3.

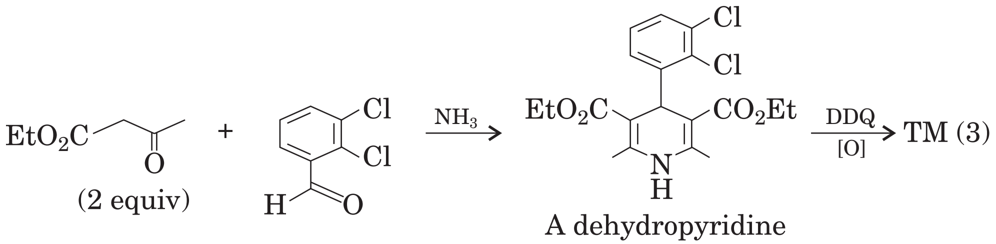


TM (3)

Retrosynthetic analysis

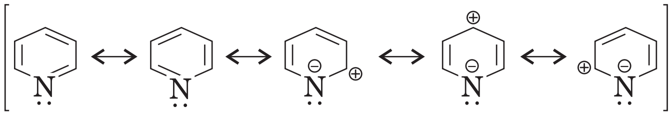


Synthesis



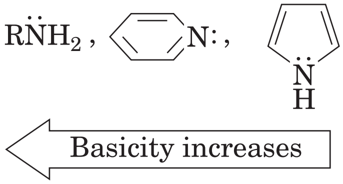
6.3.1.2 Properties and Reactions

Pyridine is a colourless liquid having boiling point 115°C. Because pyridine has a large dipole moment (2.23D), it is best regarded as a resonance hybrid of contributing Kekule and charged structures.



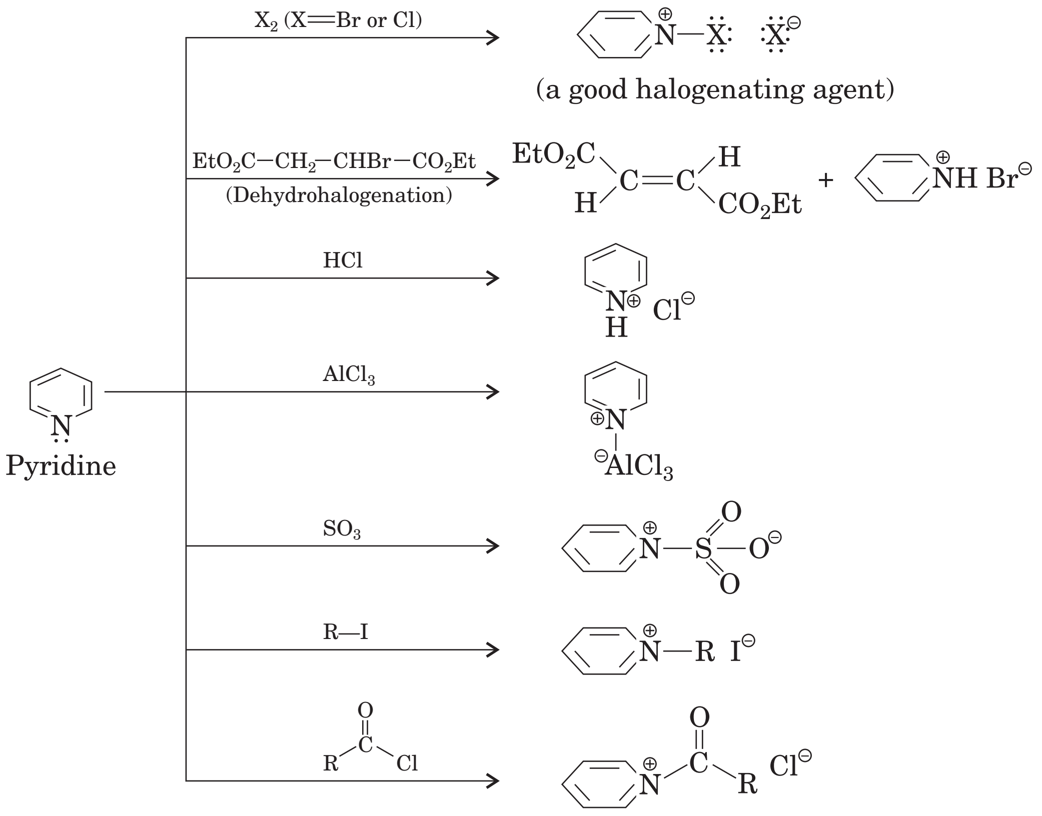
The resonance energy of pyridine from combustion data has been obtained to be 31.9 ± 2.0 kcal/mol which is less than that of benzene (36 kcal/mol). Its greater polarity accounts for its higher boiling point. Pyridine is completely soluble in water and most organic solvents. Its solubility in water is due to the presence of excellent H-bonding between pyridine and water molecules.

Pyridine is considerably basic than pyrrole, but less so than an alkylamine. As the nitrogen atom becomes progressively more multiply bonded, the lone pair is accommodated in an orbital which has more *s*-character (sp^2 as compared to sp^3 in aliphatic amines). These electrons are thus drawn closer to the nitrogen nucleus and held more tightly by it. As a consequence, the unshared pair becomes less available for coordinating with a proton with the resultant drop in basicity of pyridine as compared to aliphatic amines.



Some important reactions of pyridine are as follows:

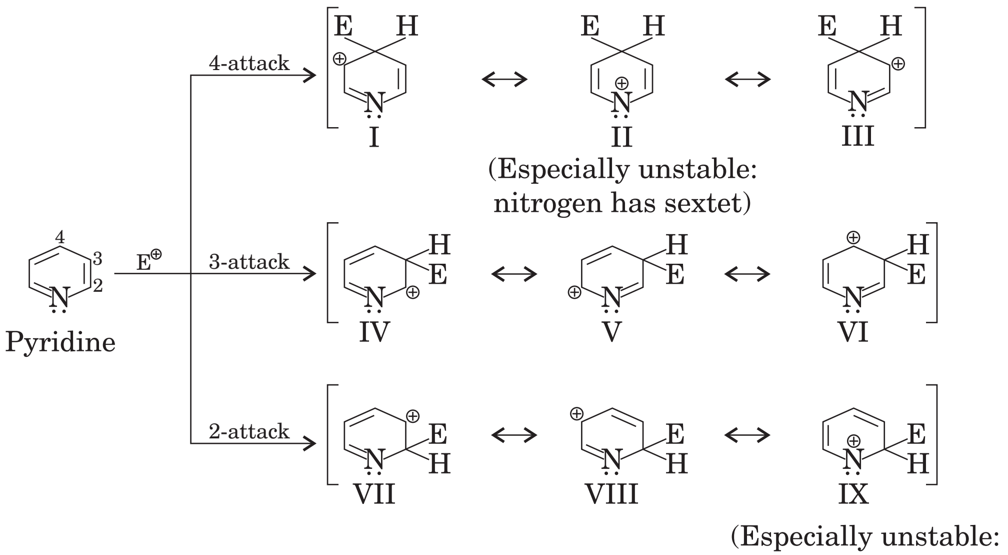
1. Reactions due to its basic property A number of reactions of pyridine take place at the nitrogen atom. The reactions in which its basic property is used are given below:



The compound obtained when pyridine reacts with acyl chloride is believed to be the active species in the acylation of hydroxyl- and amino-compounds with acyl halides in the presence of pyridine.

2. Electrophilic substitution Pyridine undergoes electrophilic substitution more slowly than benzene. An inspection of the resonance structures of pyridine makes it clear that the ring is deactivated towards electrophilic substitutions due to electron withdrawal from the ring towards the electronegative nitrogen atom. It thus follows that pyridine resembles a highly deactivated benzene derivative such as nitrobenzene towards electrophilic substitution reactions. The electrophilic substitution may thus be accomplished only with extreme difficulty and only under severe experimental conditions. A further deactivation is caused when the reaction is carried out in acidic medium and this is because protonation of the N atom results in formation of pyridinium ion.

Pyridine undergoes electrophilic substitution predominantly at the 3-position. Electrophilic attack at the 4-position of pyridine yields an intermediate ion that is a hybrid of structures I, II and III, attack at 3-position yields an ion that is a hybrid of structures IV, V and VI and attack at the 2-position forms an intermediate ion that is a hybrid of structures VII, VIII and IX.



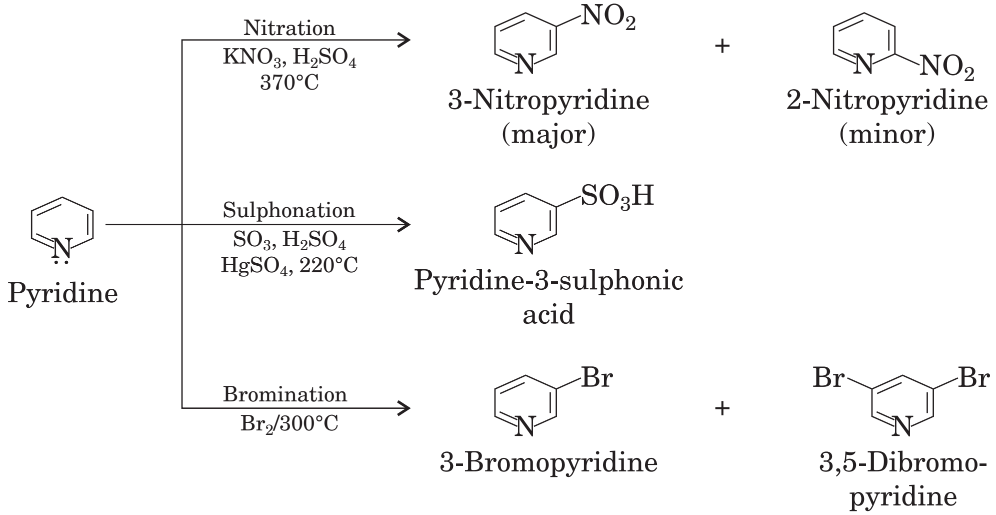
(Especially unstable: nitrogen has sextet)

(Especially unstable: nitrogen has sextet)

All these structures are less stable than the corresponding ones for attack on benzenes due to electron attraction by the N atom and it is for this reason, pyridine undergoes substitution more slowly than benzene.

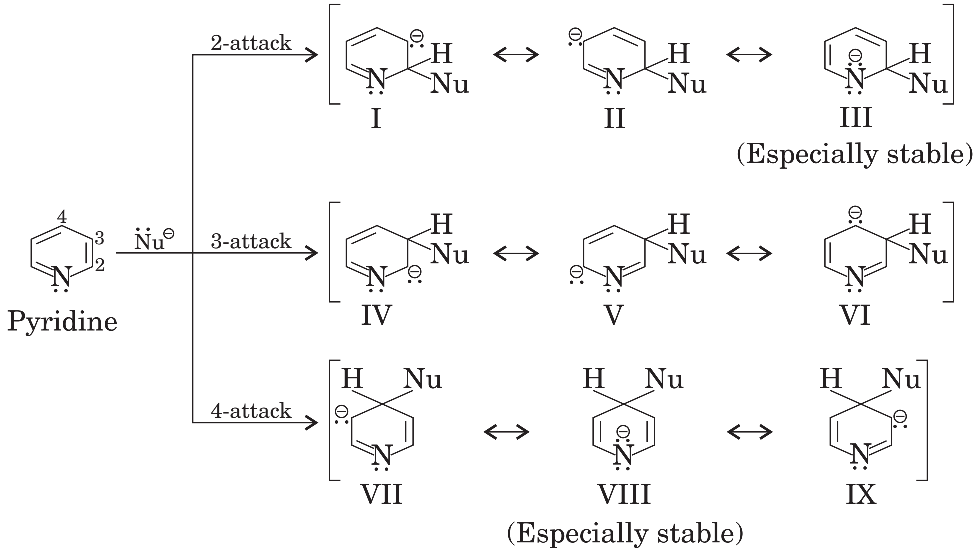
Out of these nine structures II and IX are especially unstable because in these the electronegative nitrogen atom has only a sextet of electrons. The intermediates obtained on 4- and 2-attack are, therefore, much less stable than the intermediate obtained on 3-attack which contains no such unstable resonance structure. As a result, attack at the 4-position (or 2-position) is especially slow, and substitution occurs predominantly at the 3-position.

Typical electrophilic substitution reactions of pyridine are nitration, sulphonation and bromination. It is to be noted that all these reactions are performed under drastic conditions, due to deactivation of the ring.



Pyridine does not undergo the Friedel–Crafts reaction. It forms a complex with $AlCl_3$ which is highly unreactive towards the attack by carbocations.

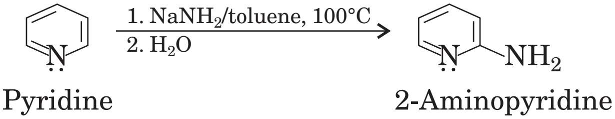
3. Nucleophilic substitution Since pyridine ring-resembles rather closely a benzene ring containing strong electron-attracting substituent (e.g., —NO_2), the most important substitution reactions of pyridine are nucleophilic substitutions. The nucleophilic substitution in pyridine takes place readily and preferentially at 2- and 4- positions. This may be explained on the basis of stabilities of the intermediate carbanions resulting from attack at different positions.



Each of the carbanion intermediates resulting from attack at 2- and 4-positions contains one especially stable resonance structure (III and VIII) in which the negative charge is accommodated by the electronegative nitrogen atom. No such especially stable structure is found in the carbanion resulting from 3-attack. The former intermediates are, therefore, more stable than the latter and because of this substitution occurs more readily and predominantly at the 2- and 4-positions than at the 3-position.

Some typical nucleophilic substitutions of pyridine are given below:

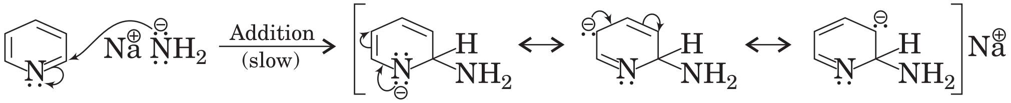
1. Chichibabin (Tschitschibabin) reaction Amination of pyridine with an alkali metal amide ($NaNH_2$ or KNH_2) is called the *Chichibabin (Tschitschibabin) reaction*. For example, when pyridine is heated with $NaNH_2$ in toluene, 2-aminopyridine is obtained.



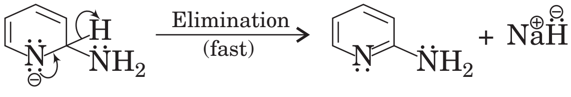
Mechanism of the reaction

When pyridine is subjected to react with strongly nucleophilic $:\overset{\ominus}{N}H_2$ ion, it undergoes nucleophilic substitution (because of its own in-built capacity for electron withdrawal) in which a hydride ion ($H^{\ominus}$) acts as the leaving group. The substitution occurs mainly at 2-position. The mechanism of the reaction involves the steps as follows:

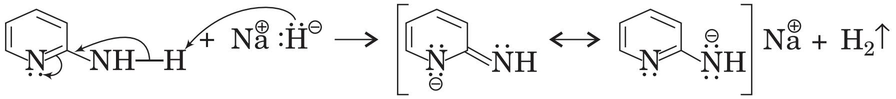
Step 1: A resonance-stabilized carbanion intermediate is formed when the nucleophile $:\overset{\ominus}{N}H_2$ attacks at the 2-position of pyridine. This is the rate-determining step of the reaction.



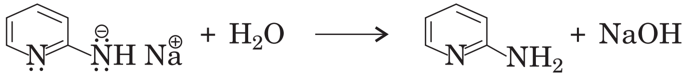
Step 2: A hydride ion ($H^{\ominus}$) is eliminated to yield 2-aminopyridine. The driving force for the elimination of the hydride ion (a poor leaving group) is the restoration of the aromaticity of the pyridine ring.



A subsequent reaction takes place in which the hydride ion (a strong base) abstracts a proton from 2-aminopyridine to form a sodio salt and H_2.

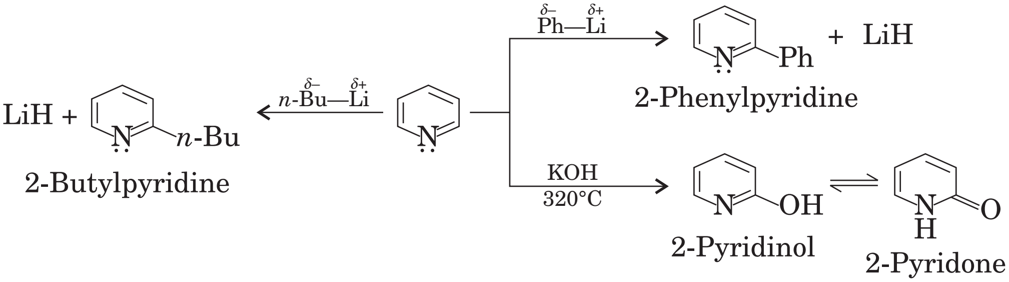


The sodio salt is finally converted to 2-aminopyridine by adding cold water to the reaction mixture.

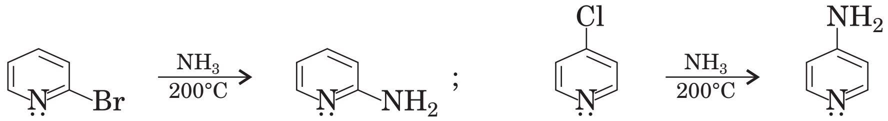


2-Aminopyridine

Some other nucleophilic substitution reactions in which hydride ion acts as the leaving group are as follows:

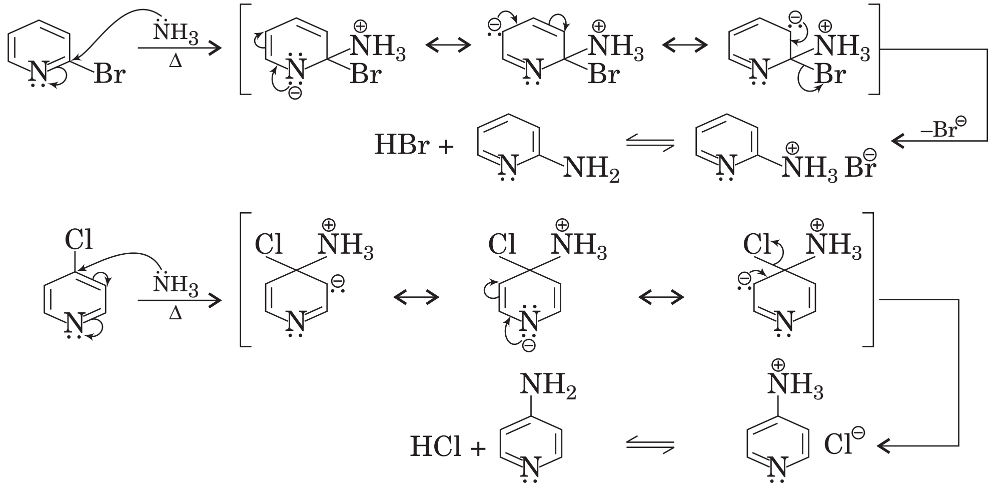


2. Displacement of halogens The activating influence of ring nitrogen atom towards nucleophilic substitution is also reflected in the facile displacement of halogens in the 2- or 4-position of pyridine. For example, when 2-bromopyridine and 4-chloropyridine is heated with NH_3 at 200°C, 2- and 4-aminopyridines are respectively obtained.

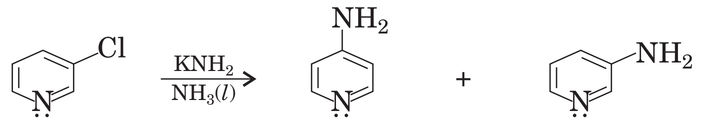


2-Bromopyridine 2-Aminopyridine 4-Chloropyridine 4-Aminopyridine

Mechanisms of the reactions

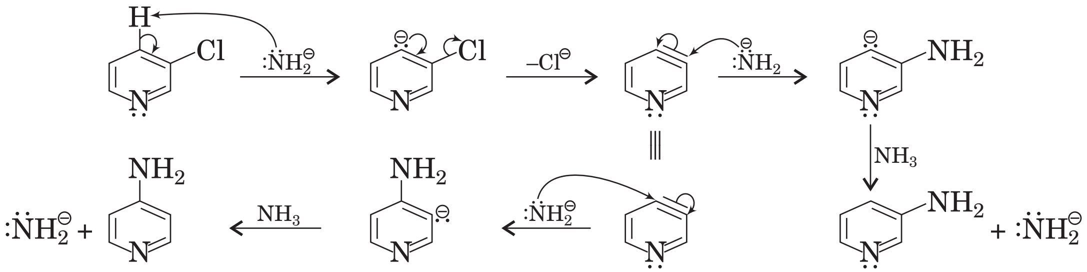


3-Halopyridines are expected to be very inert to such direct substitution reactions. However, they are attacked by strongly basic nucleophiles and the products are obtained through the formation of benzyne-like intermediates, called *pyridines*. For example:

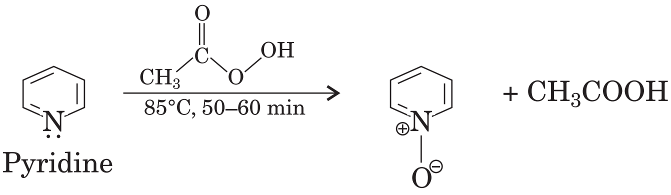


3-Chloropyridine 4-Aminopyridine 3-Aminopyridine

Mechanism of the reaction



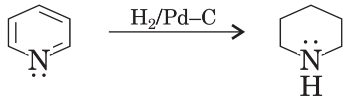
3. Oxidation When pyridine is oxidized with a peracid, such as peracetic acid or perbenzoic acid, it is converted into pyridine *N*-oxide. Because of two powerful, but opposed, polarization effects, this is a very interesting compound from the structural point of view.



Pyridine

Pyridine *N*-oxide
(53%)

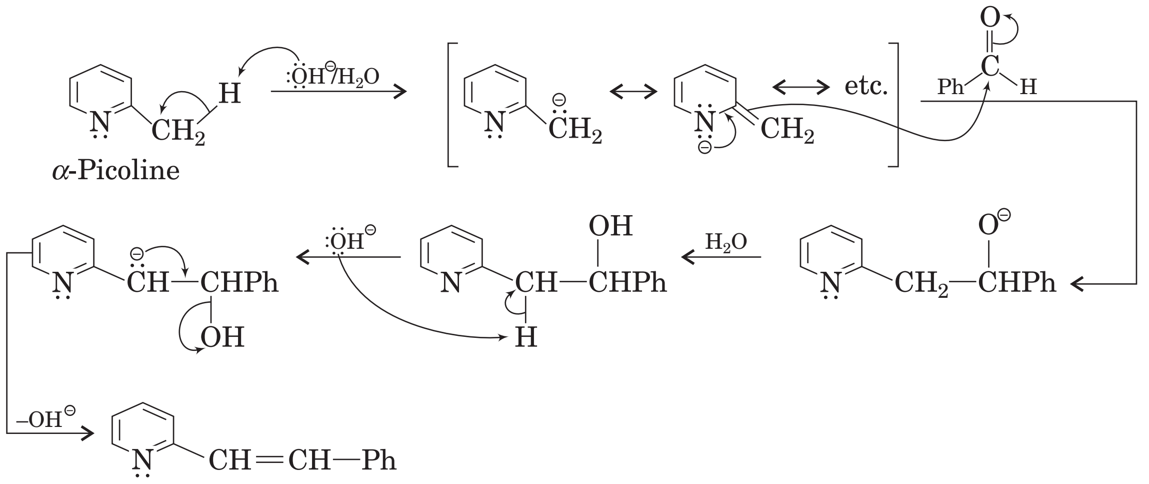
4. Reduction Catalytic hydrogenation of pyridine results in formation of the completely reduced product piperidine.



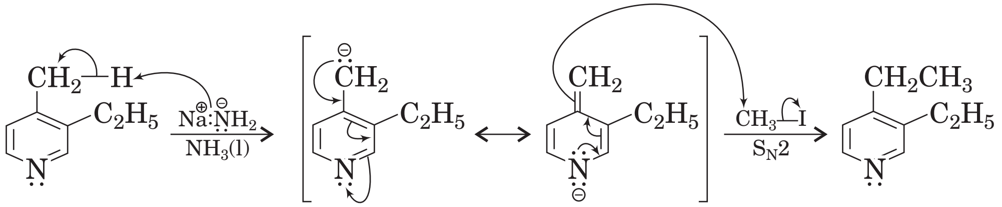
Pyridine Piperidine

Piperidine is a stronger base than pyridine and is used in a number of reactions.

5. Side chain reactivity Due to presence of electronegative nitrogen atom, the methyl hydrogens are somewhat acidic in 2- and 4-methylpyridines (commonly known as α- and γ-picolines, respectively) and consequently such pyridines undergo aldol-type condensation with aldehydes in the presence of base. The reaction of α-picoline with benzaldehyde may be outlined as follows:



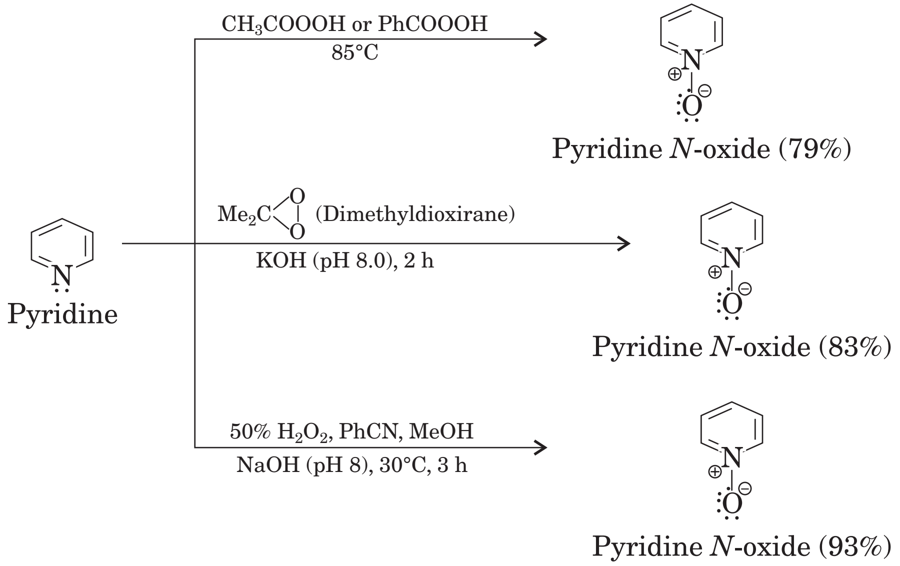
The carbanions obtained from the picolines may also undergo alkylation. For example:



6.3.2 Pyridine *N*-oxide

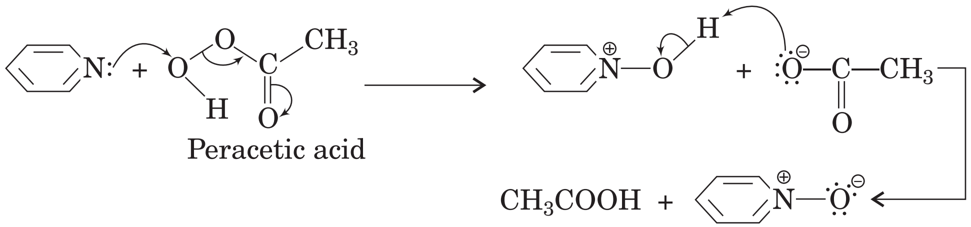
6.3.2.1 Preparations

Pyridine *N*-oxide can be prepared from pyridine by the following oxidative methods of which one is already stated.

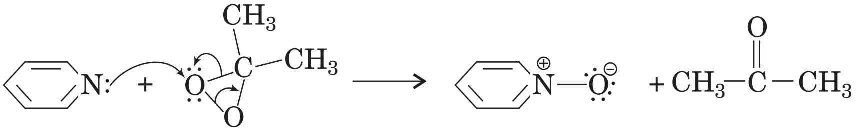


Mechanisms of the reactions

(i) **Oxidation by peracid:**



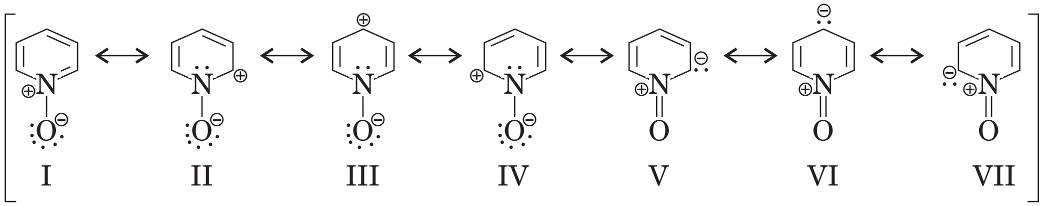
(ii) **Oxidation by dimethyldioxirane:**



6.3.2.2 *Properties and Reactions*

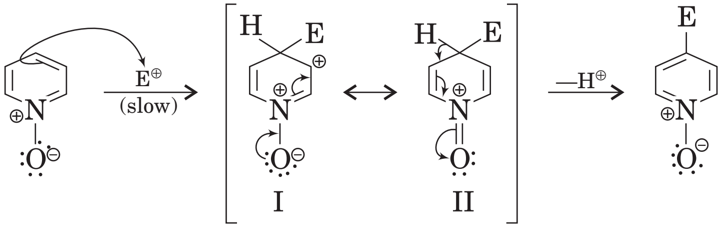
Pyridine *N*-oxide is a colourless solid having melting point 66°C. It is soluble in water and in most organic solvents.

Pyridine *N*-oxide can be represented as a resonance hybrid of the following resonance structures:

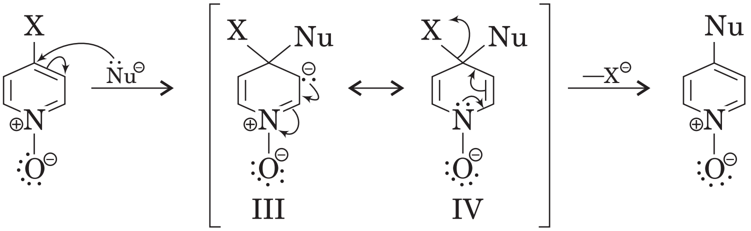


Inspection of the above structures reveals that in some canonicals (II, III and IV), there is a decrease in electron density at the various ring positions (positions 2, 4 and 6), while in other canonicals (V, VI and VII), there is an increase in electron density at these positions. For this reason, it can respond in opposite ways depending upon the demand of the reagent to which it is exposed, i.e., it is not only reactive towards electrophilic substitution but also reactive towards nucleophilic substitution.

Electrophilic substitution takes place preferably at 2- and 4-positions because it proceeds through the formation of a relatively stable intermediate containing a stable resonance structure (II) in which all atoms have complete octets. The intermediate from 3-attack cannot be stabilized in this way.

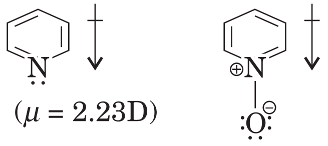


Nucleophilic substitution takes place preferably at 2- and 4-positions because it proceeds through the formation of a relatively stable intermediate containing a stable resonance structure (IV) in which the negative charge is neutralized by the positive nitrogen atom. The intermediate from 3-attack cannot be stabilized in this way.



III IV

That the donation of electrons from oxygen into the ring is significant becomes apparent from the dipole moment value. The dipole moment of pyridine is 2.23D, while that of pyridine *N*-oxide is 4.30D.

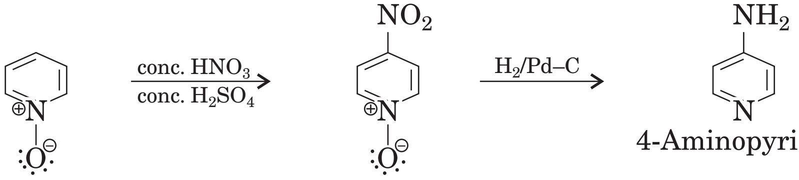


(μ = 2.23D) (μ = 4.30D)

The value is considerably lower than the sum (6.6D) of the dipole moment of pyridine and $\overset{\oplus}{N}—O^{\ominus}$ bond moment. It, thus, follows that the structures V, VI and VII contribute significantly towards the hybrid.

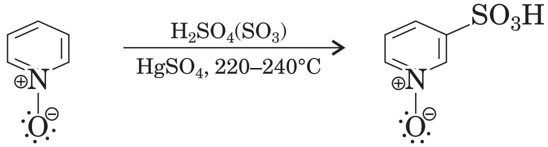
Some important reactions of pyridine *N*-oxide are given below:

1. Nitration Pyridine *N*-oxides are nitrated more easily than the parent pyridines. Nitration of pyridine *N*-oxide with mixed acid gives a high yield of 4-nitropyridine *N*-oxide. It can be converted to 4-aminopyridine by catalytic hydrogenation.



Pyridine *N*-oxide 4-Nitropyridine *N*-oxide 4-Aminopyridine

2. Sulphonation Sulphonation of pyridine *N*-oxide takes place only under very drastic conditions and 3-pyridine *N*-oxide sulphonic acid is obtained.

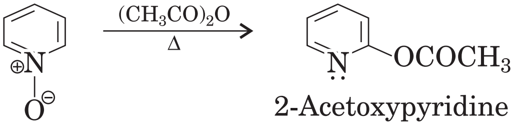


Pyridine *N*-oxide

3-Pyridine *N*-oxidesulphonic acid

The change in orientation in sulphonation is due to the formation of a species $(\overset{\oplus}{\text{Py}}\text{—}\,\text{OSO}_3^{\ominus})$ in which the electron-donating property of the oxygen atom is suppressed.

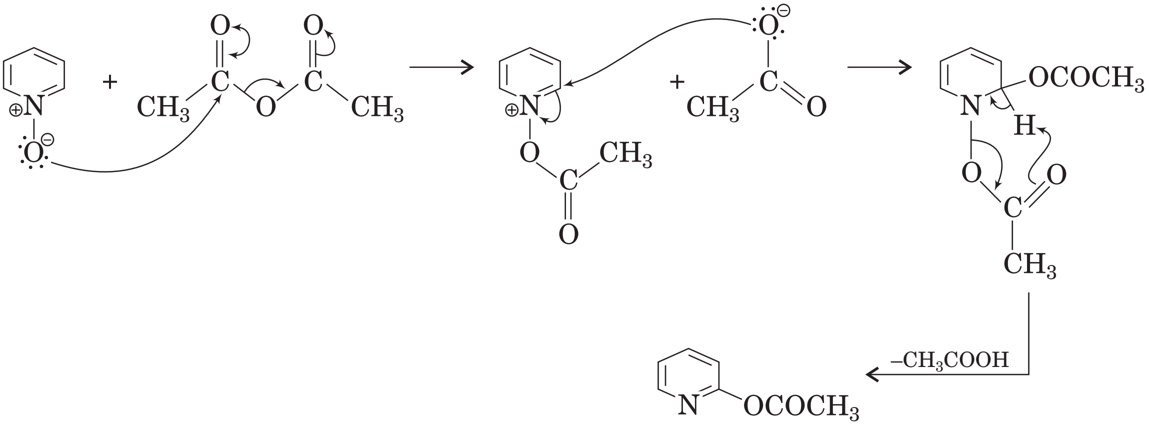
3. Reaction with acetic anhydride When pyridine *N*-oxide is heated with acetic anhydride, 2-acetoxypyridine is obtained.



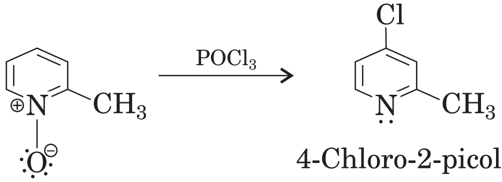
2-Acetoxypyridine

Pyridine *N*-oxide

Mechanism of the reaction



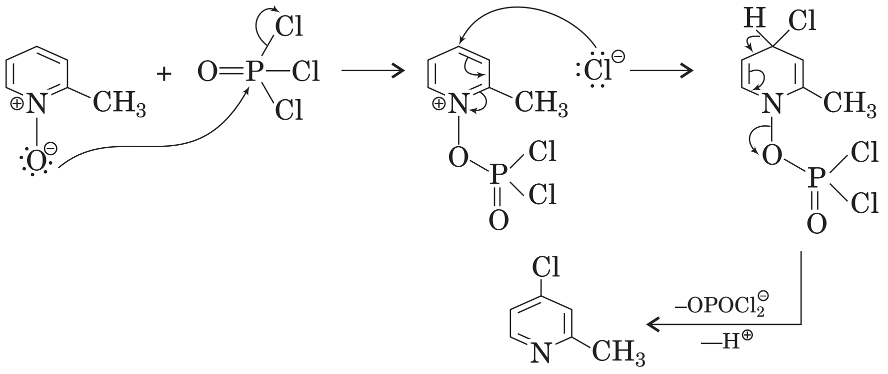
4. Reaction with phosphorus oxychloride Phosphorus oxychloride reacts with pyridine *N*-oxides to form chloropyridines. For example:



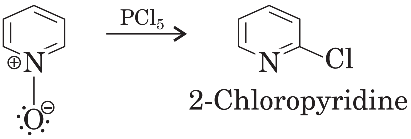
4-Chloro-2-picoline

2-Picoline *N*-oxide

Mechanism of the reaction

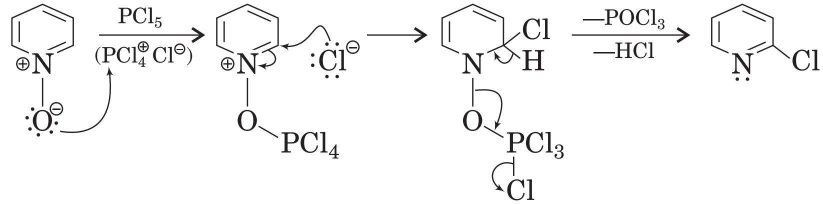


5. Reaction with phosphorus pentachloride Pyridine *N*-oxide reacts with PCl_5 to form 2-chloropyridine predominantly.

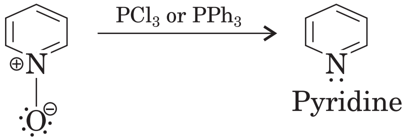


2-Chloropyridine

Mechanism of the reaction:

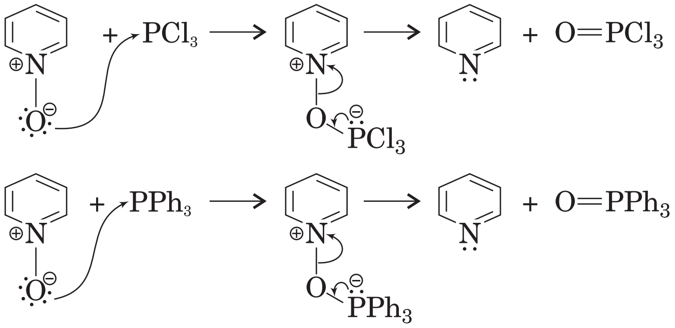


6. Conversion into parent pyridine Pyridine *N*-oxide can be converted into the parent pyridine by treating with phosphorus trichloride (PCl_3) or triphenylphosphine.

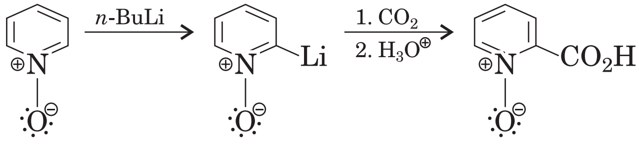


Pyridine

Mechanisms of the reactions

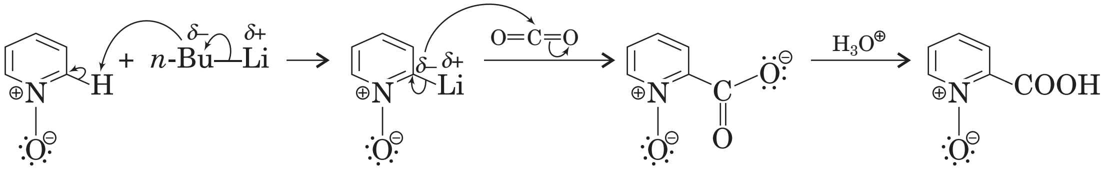


7. Ring lithiation When pyridine *N*-oxide is treated with *n*-butyllithium, ring lithiation occurs at the 2-position. The lithiated compound can produce the corresponding carboxylic acid by reacting with CO_2 followed by acidification



Pyridine *N*-oxide

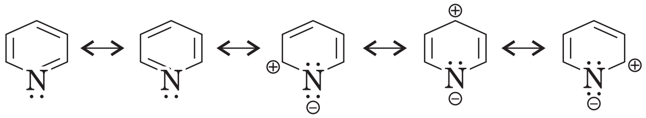
Mechanism of the reactions



SOLVED PROBLEMS

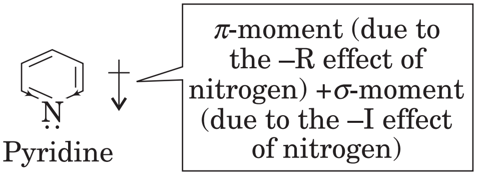
1. The dipole moment of pyridine is much greater than that of piperidine. Explain.

Solution Pyridine can be represented as a resonance hybrid of the following five canonicals (two equivalent Kekule structures and three zwitterionic structures with the negative charge on electronegative nitrogen atom).



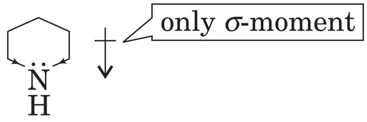
Resonance structures of pyridine

From the charged structures it becomes evident that the π-moment operates in the same direction as the σ-moment and the net moment is additive. In piperidine, on the other hand, only the σ-moment of operates. Because of this, the dipole moment of pyridine is substantially greater than that of piperidine.



π-moment (due to the –R effect of nitrogen) +σ-moment (due to the –I effect of nitrogen)

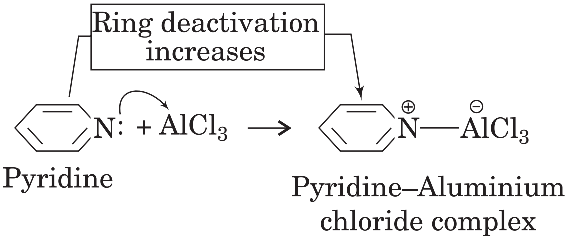
Pyridine
(μ = 2.26D)

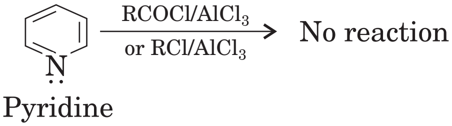


Pipyridine
(μ = 1.17D)

2. Pyridine does not undergo the Friedel–Crafts reaction—Why?

Solution Pyridine acts as a Lewis base and forms a complex with the Lewis acid $AlCl_3$. The ring of the complex becomes highly deactivated due to the positive charge on the nitrogen atom, and as a consequence, it becomes unreactive towards attack by a carbocation (or an acylium ion), the electrophile involved in the Friedel–Crafts reaction.


Ring deactivation increases
N:
+ AlCl3
N
AlCl3
Pyridine
Pyridine–Aluminium chloride complex



3. Explain the following observations:

(a) 4-Chloro-3-nitropyridine undergoes hydrolysis readily even in warm water.

(b) The reactivity order of decarboxylation of isomeric pyridinecarboxylic acids is 2 > 3 > 4, whereas the order of reactivity in case of isomeric pyridineacetic acids is 2 or 4 > 3.

(c) Pyridine is less basic than piperidine.

(d) Pyridine resembles nitrobenzene (a highly deactivated benzene derivative) towards electrophilic and nucleophilic substitution reactions.

(e) The dipole moment of pyridine is less than that of 4-amino-pyridine but more than that of 4-cyanopyridine.

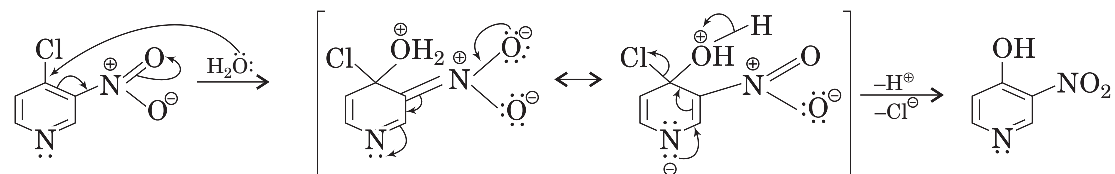
(f) Nitration and sulphonation of pyridine require drastic conditions.

(g) Unlike furan and pyrrole, pyridine does not undergo polymerization in the presence of strong acid.

(h) Pyridine boils at a much higher temperature than benzene, even though they have comparable molecular masses.

Solution

(a) Because of the cumulative electron-withdrawing (–R) effect of the ring nitrogen and the nitro group present at the *ortho*-position of the departing chlorine atom, the hydrolysis of 4-chloro-3-nitropyridine takes place readily even in warm water (a weak nucleophile).

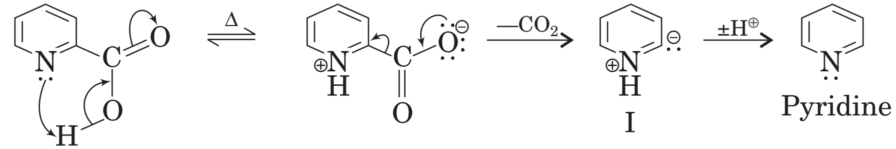


4-Chloro-3-nitropyridine

(a stable intermediate: the negative charge is on electronegative nitrogen and oxygen atoms)

4-Hydroxy-3-nitropyridine

(b) Decarboxylation of a pyridinecarboxylic acid takes place through the formation of zwitterion (I) in which the negative charge on carbon is stabilized the –I effect of the positively charged nitrogen atom. For example:

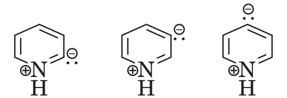


2-Pyridinecarboxylic acid

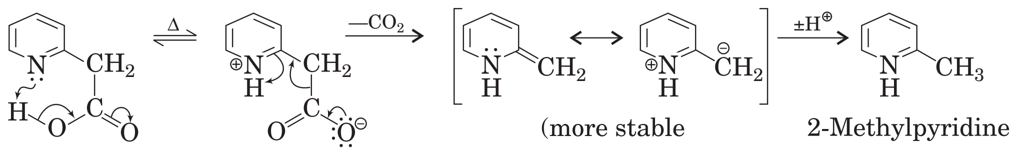
I

Pyridine

Since the inductive effect becomes weaker with distance, the carbanion obtained from 2-acid is more stable than that obtained from 3-acid which, in turn, is more stable than that obtained from 4-acid.



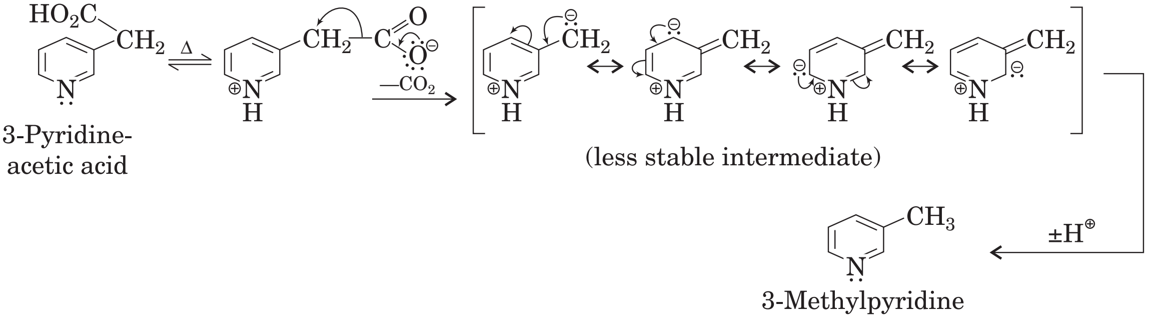
Because of this, the order of reactivity towards decarboxylation of pyridinecarboxylic acids is: 2-acid > 3-acid > 4-acid. When 2- or 4-phenylacetic acid undergoes decarboxylation, the benzylic-like intermediate carbanion is stabilized by resonance involving a neutral canonical form. The carbanion obtained from 3-acid is not stabilized by such resonance involving a neutral canonical, and therefore, it is less stable. For this reason, the order of reactivity of the isomeric pyridineacetic acids towards decarboxylation is: 2- or 4-acid > 3-acid.



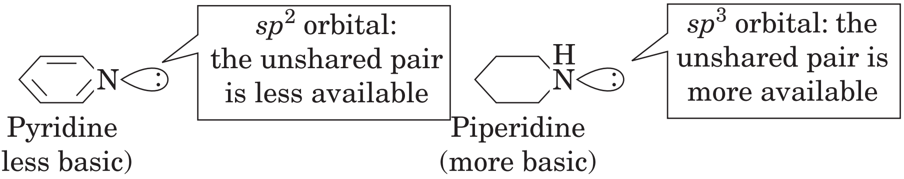
2-Pyridineacetic acid

(more stable intermediate)

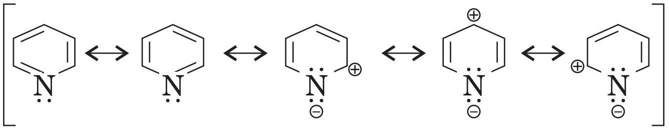
2-Methylpyridine



(c) The nitrogen atoms in pyridine and piperidine in all the occurrences are sp^2 and sp^3 hybridized respectively and so, the unshared pair of electrons on nitrogen occupies sp^2 (having 33.33% *s* character) and sp^3 (having 25% *s* character) orbitals, respectively. Since electrons in an *s* orbital are held more tightly to the nucleus than electrons in a *p* orbital, the unshared pair of electrons in hybrid orbitals with large *s* character is attracted towards nitrogen nucleus with greater force and is less available for coordinating with a proton. Therefore, pyridine in which the nonbonding pair of electrons on nitrogen occupies an orbital having more *s* character is less basic than piperidine.

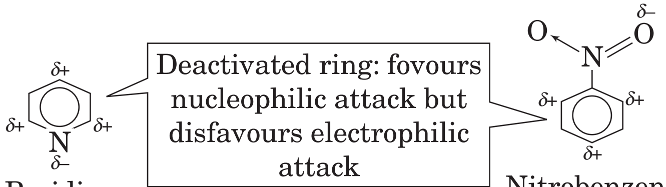

sp² orbital: the unshared pair is less available
sp³ orbital: the unshared pair is more available
Pyridine (less basic)
Piperidine (more basic)

(d) Pyridine can be represented as a resonance hybrid of the following canonicals:



Resonance structures of pyridine

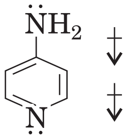
An inspection of this structure makes it clear that the electronegative nitrogen atom withdraws electrons from the ring and causes π-deficiency at carbon atoms, i.e., makes it a π-deficient heterocycle and as a result, the ring becomes deactivated towards electrophilic substitution but activated towards nucleophilic substitution. Thus, electrophilic attack on pyridine takes place only under vigorous conditions whereas it undergoes nucleophilic attack rather easily. Pyridine, therefore, resembles a highly deactivated benzene derivative like nitrobenzene towards electrophilic and nucleophilic substitution reactions.



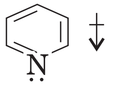
Deactivated ring: fovours nucleophilic attack but disfavours electrophilic attack

Pyridine Nitrobenzene

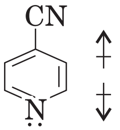
(e) 4-Aminopyridine has a larger dipole moment than pyridine because in the former the moment due to ring nitrogen and the moment due to the —NH_2 group (the unshared pair of electrons on nitrogen remains in proper conjugation with the ring nitrogen) point in the same direction. On the other hand, 4-cyanopyridine has a lower dipole moment than pyridine, because in the former the moment due to the —CN group and the moment due to the ring nitrogen point in opposite directions and thereby cancels each other partially.



4-Aminopyridine
(μ = 4.40 D)



Pyridine
(μ = 2.26 D)



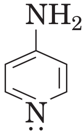
4-Cyanopyridine
(μ = 1.60 D)

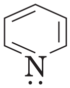
(f) The electronegative nitrogen atom withdraws electrons from the ring carbons of pyridines (by –R effect from 2-, 4- and 6 positions and by –I effect from all five positions). As a result, the ring becomes deactivated towards electrophilic attack. Again, nitration and sulphonation reactions are carried out in strong acidic medium, and in such a medium, protonation of the nitrogen atom occurs to form a pyridinium ion. Formation of pyridinium ion causes the ring carbons to be more positive, i.e., causes a further deactivation. Because of this, pyridine is difficult to nitration and sulphonation and these reactions require drastic conditions to take place.

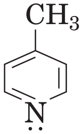
(g) Unlike π-excessive furan and pyrrole, pyridine with a deactivated ring does not undergo protonation at the ring carbons and because of this, it does not undergo polymerization in the presence of strong acid.

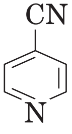
(h) Since pyridine is a polar molecule, therefore, there operates stronger dipole-dipole attraction among the molecules of pyridine. Benzene, on the other hand, is a nonpolar (μ = 0D) molecule and there operates weaker van der Waals attractive forces among the molecules of benzene. It is for this reason the boiling point of pyridine is much higher (115°C) than that of benzene (80°C) even though their molecular masses are comparable (79 and 78).

4. **Arrange the following compounds in order of increasing basicity and explain the order:**


I

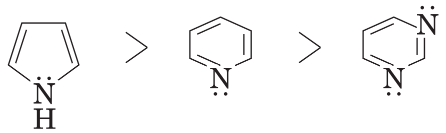

II


III

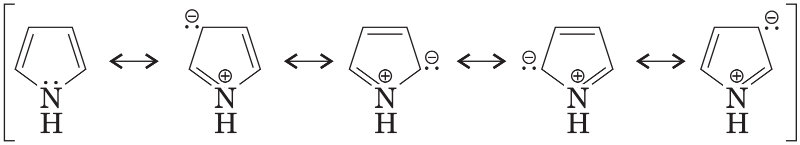

IV

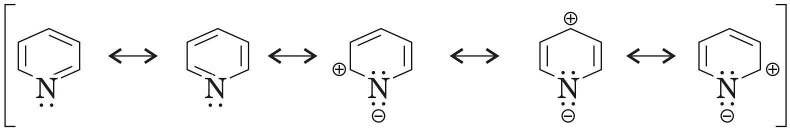
Solution The increasing order of basicity of the given compounds is: IV < II < III < I. Since the amino (—NH_2) group is more electron-releasing (by +R effect) than the methyl group (by +I and hyperconjugation) the electron density on ring nitrogen is much higher in I than in III and so, I is more basic than III. III is more basic than II because it contains no ring substituent. The electron-withdrawing —CN group withdraws electrons from the ring nitrogen by –R effect. As a result, the electron density on nitrogen in compound IV is considerably reduced, and so, it is less basic than II.

5. **Explain the following order of reactivity towards electrophilic substitution:**

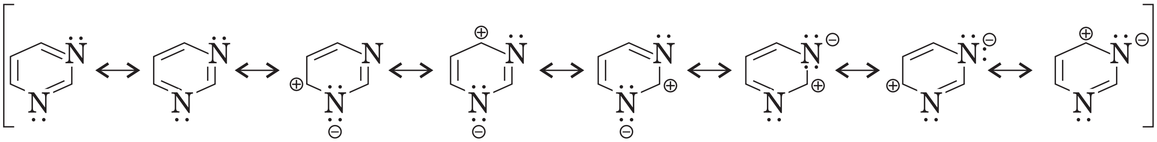

Pyrrole Pyridine Pyrimidine

Solution Pyrrole and pyridine can be represented as a resonance hybrid of the following resonance structures:


Resonance structures of pyrrole


Resonance structures of pyridine

The unshared pair of electrons on nitrogen in π-excessive pyrrole molecule makes the ring carbon negatively polarized by donating electrons towards the ring for maintaining the aromatic sextet. The ring is thus activated towards electrophilic substitution. On the other hand, the ring nitrogen in pyridine makes the ring carbons positively polarized by withdrawing electrons. The ring is, thus, deactivated towards electrophilic substitution. A second nitrogen atom in pyrimidine makes the ring relatively more deactivated due to the same basic reason (positive polarization of the carbon atoms becomes double).

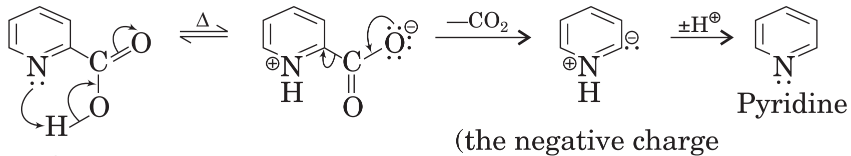


Resonance structures of pyrimidine

Therefore, the order of reactivity of these three compounds towards electrophilic substitution is as follows: pyrrole > pyridine > pyrimidine.

6. **Predict the products expected to be formed when pyridine-2-carboxylic acid is heated in the presence and in absence of PhCHO and explain.**

Solution When pyridine-2-carboxylic acid is heated, it undergoes decarboxylation to give pyridine through the formation of a zwitterionic intermediate as follows:

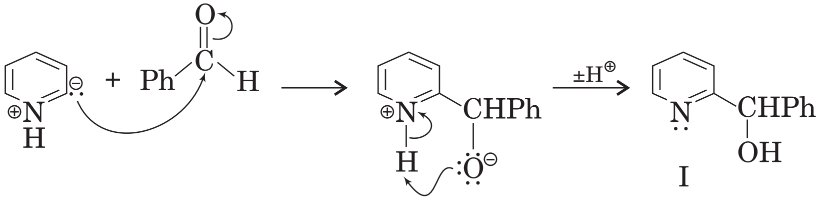


Pyridine-2-carboxylic acid

Pyridine

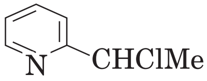
(the negative charge is stabilized by the adjacent positive charge)

When the decarboxylation reaction is carried out in the presence of acetone, the zwitterionic intermediate reacts with acetone to yield the secondary alcohol I as follows:

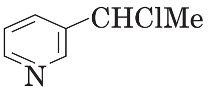


I

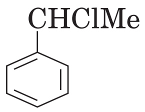
7. **Account for the following observations:**
   (a) **2,6-Di-*tert*-butylpyridine is a specific proton scavenger.**
   (b) **Sulphonation of 2,6-di-*tert*-butylpyridine can be easily effected with SO_3 at –10°C, whereas pyridine cannot be sulphonated under such conditions.**
   (c) **S_N1 reactivity of the following compounds decreases in the order: IV > III > II > I.**



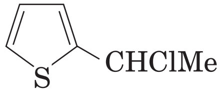
I



II

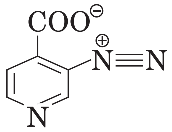


III



IV

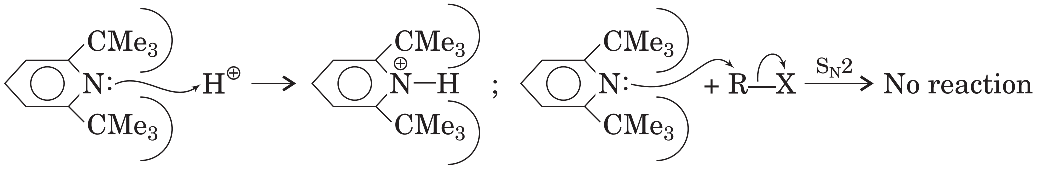
(d) When the following compound is heated, two isomeric compounds (molecular formula $C_{10}H_6N_2$) are obtained:



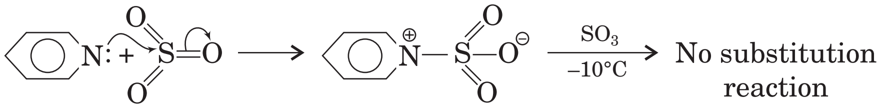
(e) When *N*-methylpyridinium iodide is heated at 300°C, it undergoes a rearrangement to yield 2- and 4-methylpyridine.

Solution

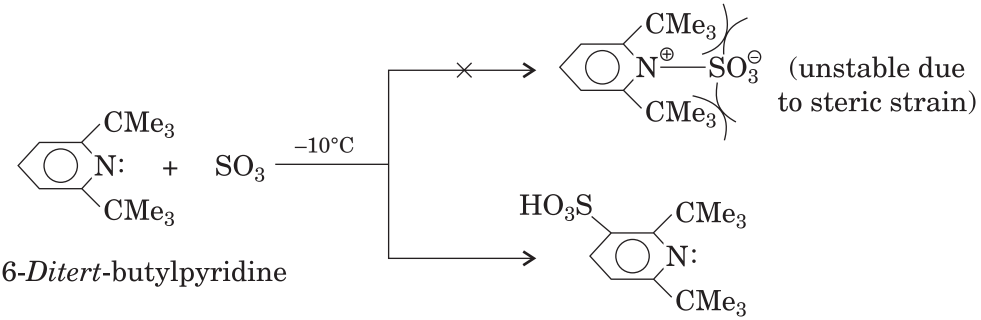
(a) Because of steric reason 2,6-di-*tert*-butylpyridine does not act as a nucleophile. However, it can take up a small proton. So, it is a specific proton scavenger.



(b) Sulphur trioxide reacts with pyridine to form an adduct in which the ring becomes further deactivated towards elctrophilic substitution. Because of this, pyridine does not undergo sulphonation when treated with SO_3 at –10°C. Because of steric hindrance caused by the two bulky *tert*-butyl groups adjacent to ring nitrogen, adduct formation does not take place in the case of 2,6-di-*tert*-butylpyridine. As a consequence, unlike pyridine ring deactivation does not take place and so, sulphonation takes place rather easily.



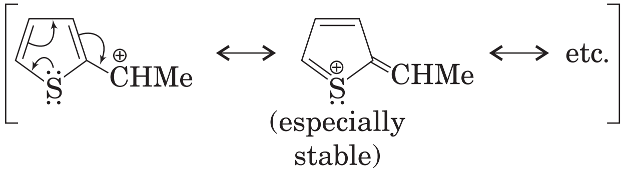
Pyridine



2,6-*Ditert*-butylpyridine

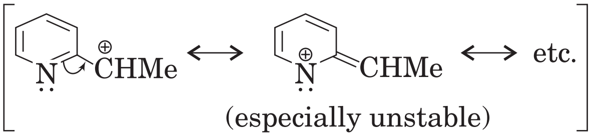
2,6-Di-*tert*-butylpyridine-3-sulphonic acid

(c) It is the stability of the carbocation intermediate on which the S_N1 reactivity of a compound depends. Let us take the carbocation ($\mathrm{Ph\overset{\oplus}{C}HMe}$) obtained from III as the standard for comparison. The carbocation obtained from IV is more stable than that obtained from III because the positive charge is relatively more stabilized by resonance (the hybrid contains a very stable resonance structure in which all the atoms have their octet filled up).

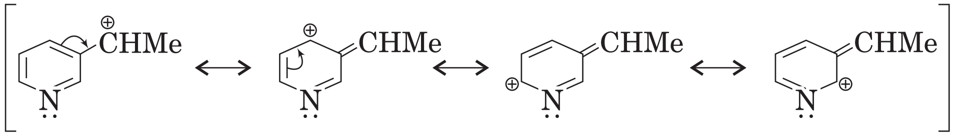


(the intermediate carbocation obtained from IV)

The carbocation obtained from I and II are less stable than that obtained from III because the electron-attracting N atom makes the ring positive, deterring the introduction of +ve charge. Of the two isomeric carbocations obtained from I and II, the one obtained from I is less stable because it has a high-energy (less stable) resonance structure with the +ve charge on N holding only six electrons. The carbocation obtained from II has no resonance structure with an electron-deficient (sextet) N atom.

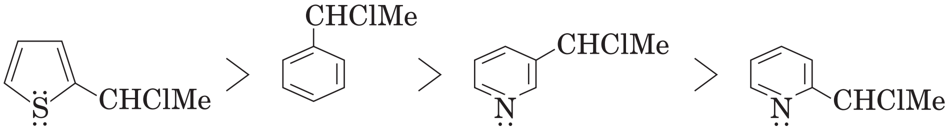


(the carbocation obtained from I)



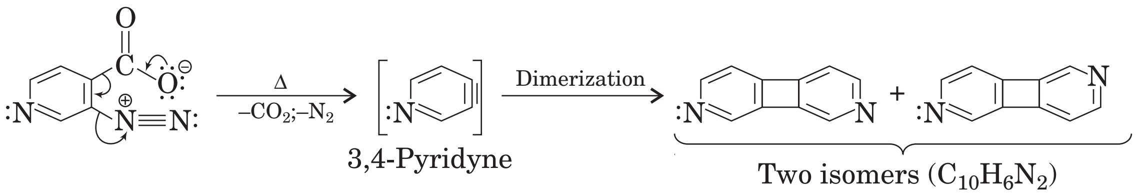
(the carbocation obtained from II)

Therefore, the decreasing order of stability of the intermediate carbocations is as follows: from IV > from III > from II > from I. Hence, the decreasing order of S_N1 reactivity of the given chloro compounds is

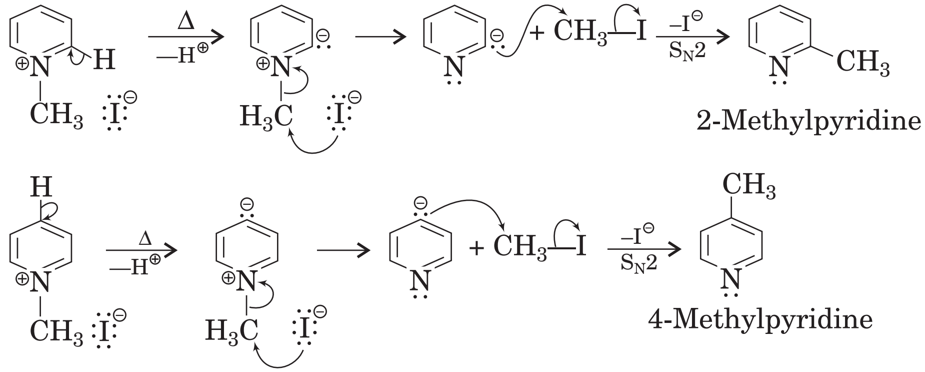


IV III II I

(d) When pyridinediazonium carbonate is heated, it undergoes decomposition to produce 3,4-pyridyne which subsequently dimerizes to yield two isomeric compounds.

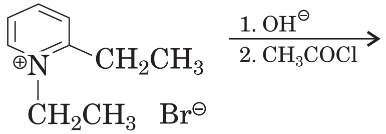


(e) When *N*-methylpyridinium iodide is heated, it undergoes *Ladenburg rearrangement* to yield 2- and 4-methylpyridine as follows:

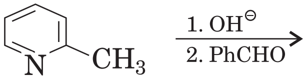


8. Predict the product and suggest a mechanism for each of the following reactions:

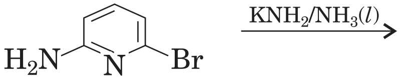
(a)



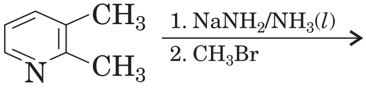
(b)



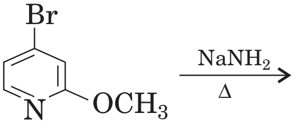
(c)



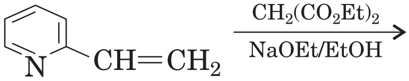
(d)



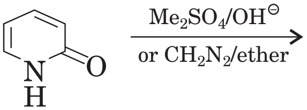
(e)



(f)

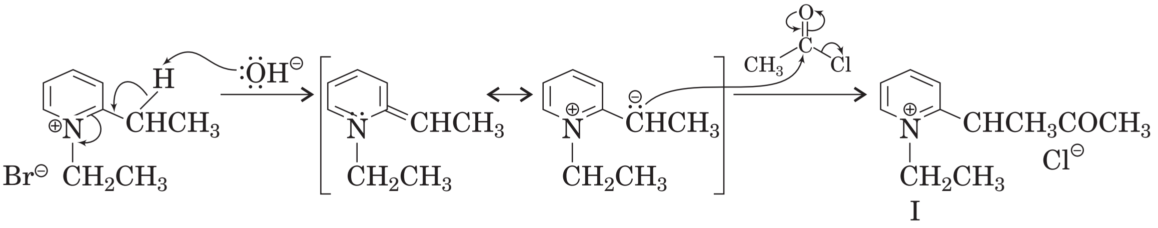


(g)

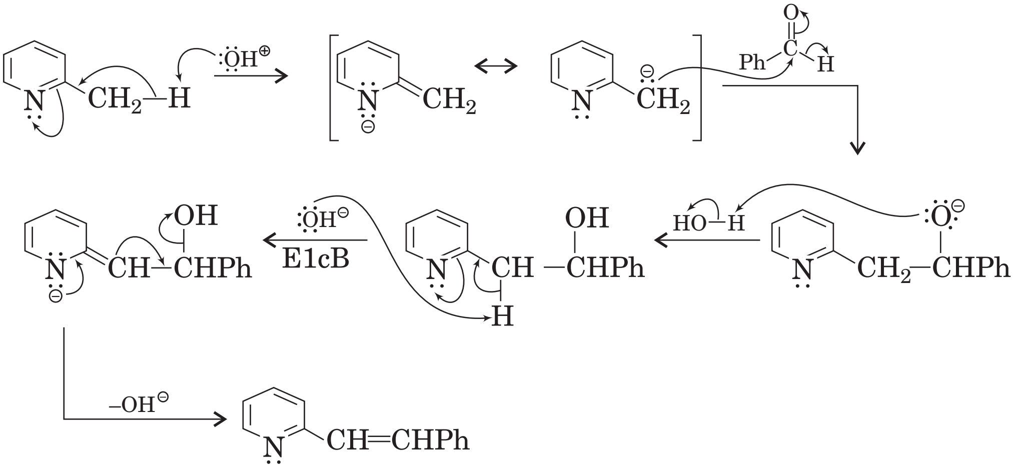


Solution

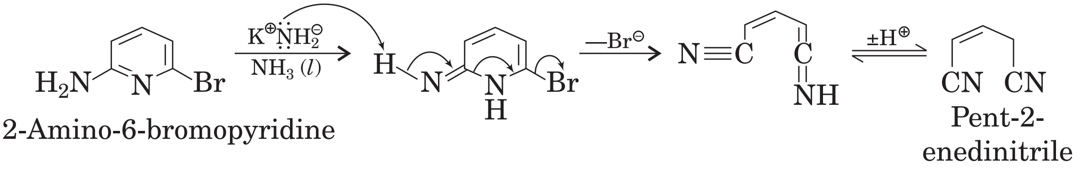
(a) Base abstracts one methylene hydrogen (which is considerably acidic) of the ethyl group attached to C-2. The resonance-stabilized carbanion then reacts with acetyl chloride to form the salt I.



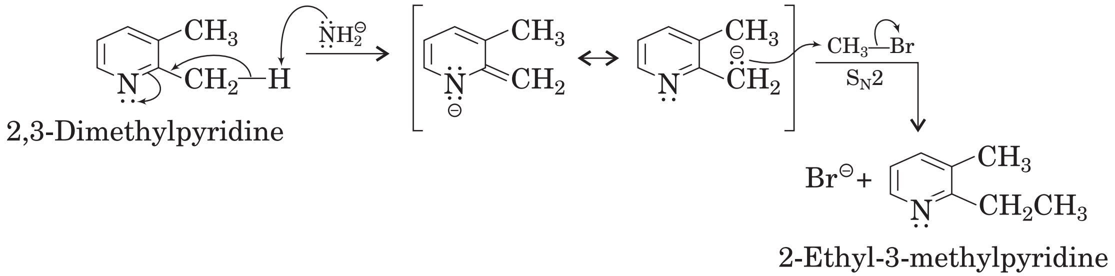
(b) Since the conjugate base of α-picoline is stabilized by resonance, the methyl hydrogens are somewhat acidic, and consequently, it undergoes aldol type condensation with benzaldehyde in the presence of base.



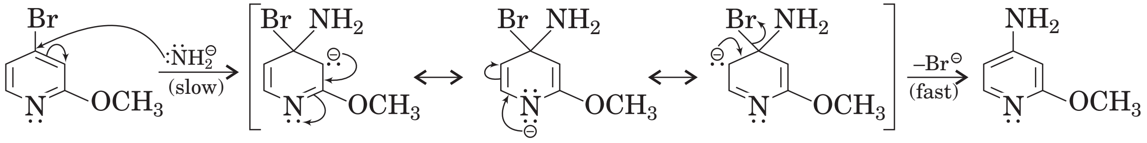
(c) The compound undergoes ring-opening reaction in the presence of strong base $NH_2^{\ominus}$ to form a dinitrile.



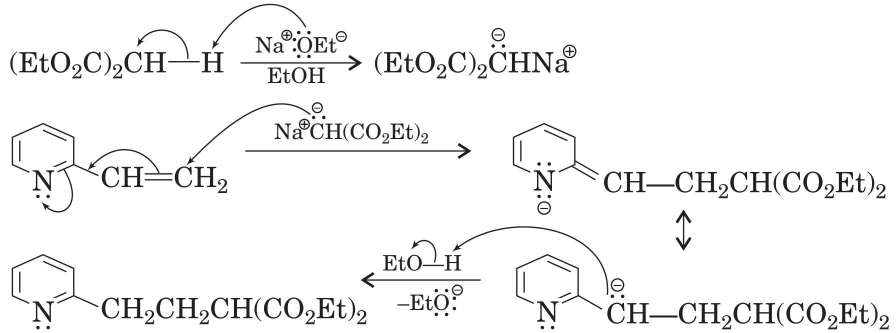
(d) The hydrogens of the C-2 methyl group is relatively more acidic than the hydrogens of the C-3 methyl group because the conjugate base is more stabilized by resonance involving a canonical form in which the electronegative N atom can accommodate the negative charge. For this reason, the C-2 methyl group undergoes methylation by CH_3Br in the presence of strong base $NH_2^{\ominus}$.



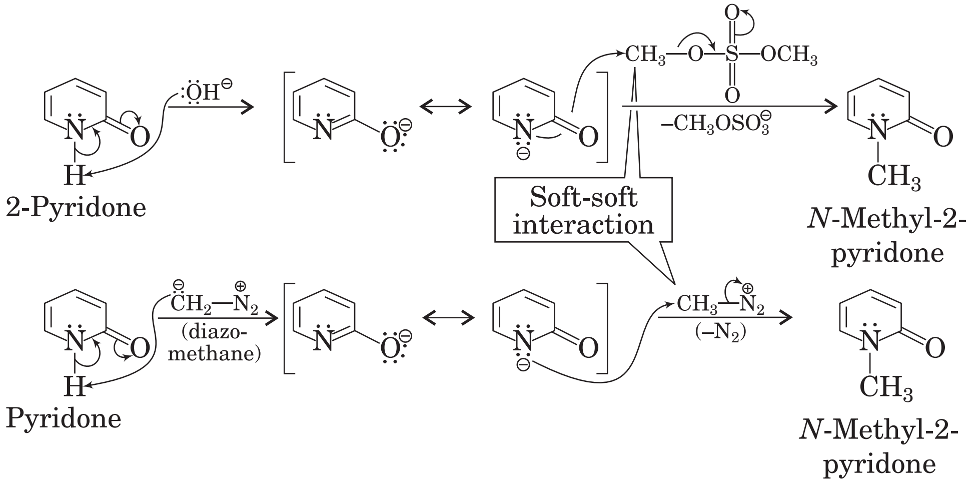
(e) Since the bromine atom is situated at C-4, this pyridine derivative undergoes nucleophilic aromatic substitution to give 4-amino-2-methoxypyridine.



(f) Because of stabilization of the carbanionic centre at pyridine *α*-position, 2-vinylpyridine undergoes Michael type addition to give the corresponding product.

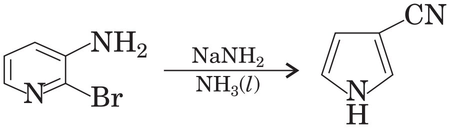

$(EtO_2C)_2CH—H$
Na⊕ :ÖEt⊖
EtOH
$(EtO_2C)_2\ddot{C}HNa^{\oplus}$
$Na^{\oplus}\ddot{C}H(CO_2Et)_2$
EtO—H
–EtÖ:⊖

(g) 2-Pyridone undergoes *N*-methylation to yield *N*-methyl-2-pyridone when treated with $Me_2SO_4/OH^{\ominus}$ or CH_2N_2/ether. The mechanisms of these reactions may be outlined as follows:

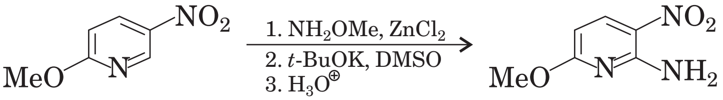


9. Suggest reasonable mechanisms for the following transformations:

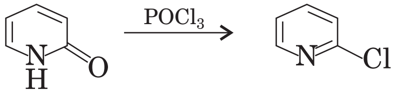
(a)



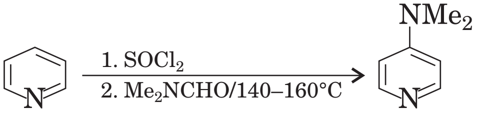
(b)



(c)

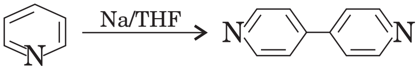


(d)



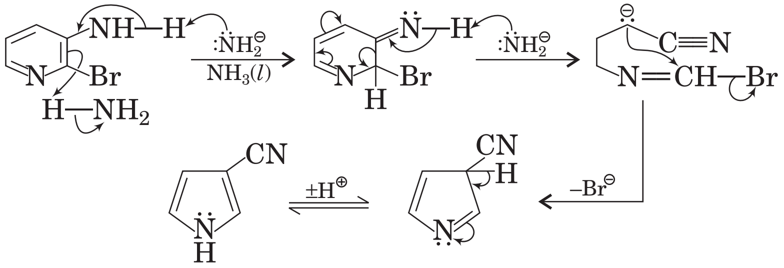
(C.U. 2014)

(e)

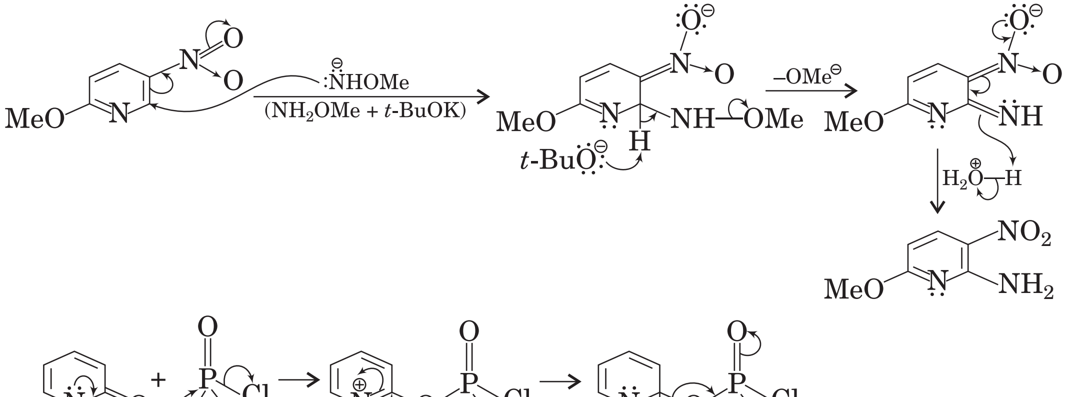


Solution

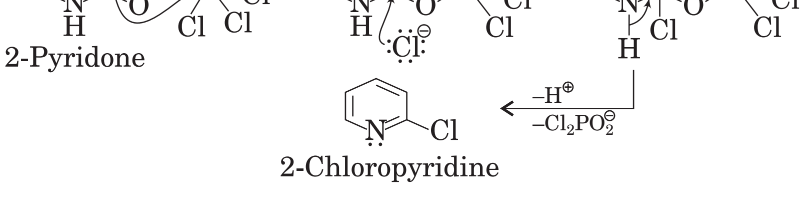
(a)



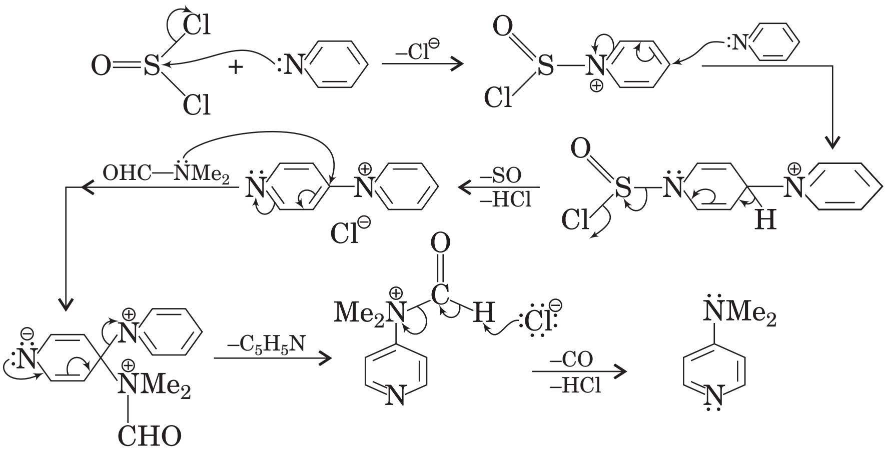
(b)



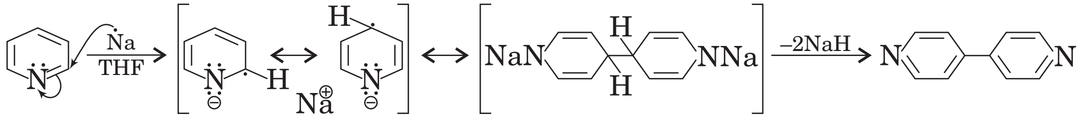
(c)



(d)



(e) Sodium brings about 'oxidative dimerization' to yield 4,4′-bipyridine.



10. Account for the following observations:

(a) Methyl hydrogens of 2- and 4-picolines are more acidic than the methyl hydrogens of 3-picoline. [C.U. 2014]

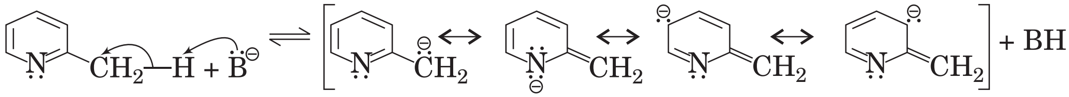
(b) 2- and 4-Chloropyridines undergo nucleophilic aromatic substitution when treated with NaOEt, whereas 3-chloropyridine does not.

(c) 2-Pyridone reacts with benzyl chloride in the presence of base to yield *N*-benzyl-2-pyridone as the major product. However, when 6-methyl-2-pyridone is allowed to react with benzyl chloride in the presence of a base, 2 benzyloxypyridine is obtained as the major product.

(d) Electrophilic substitution in 4-phenylpyridine occurs in the benzene ring.

Solution

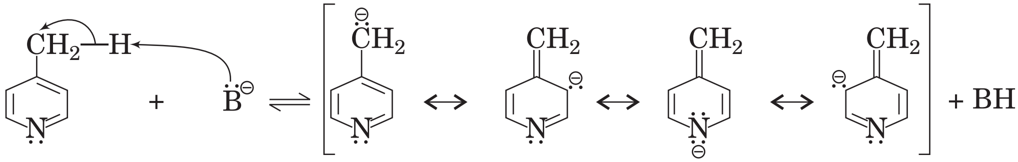
(a) The conjugate bases of 2- and 4-picolines are relatively more resonance stabilized than the conjugate base of 3-picoline because in one of their resonance structures the negative charge is placed on the electronegative N atom. For this reason, the methyl hydrogens of 2- and 4-picolines are more acidic than the methyl hydrogens of 3-picoline.



2-Picoline

(especially stable)

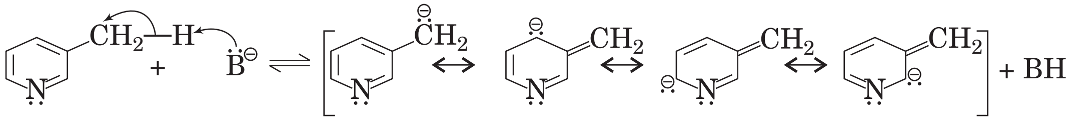
Conjugate base of 2-picoline



4-Picoline

(especially stable)

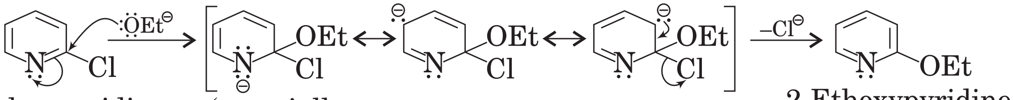
Conjugate base of 4-picoline



3-Picoline

Conjugate base of 3-picoline
(contains no especially stable structure and
so less stable than the other two)

(b) The anionic intermediate involved in nucleophilic aromatic displacement of 2- and 4-chloropyridines are relatively more stable than that involved in the case of 3-chloropyridine because in one of their resonance structures the negative charge is placed on the electronegative N atom. Nucleophilic attack at C-3 places the negative charge only on less electronegative carbons. For this reason, when treated with sodium ethoxide, 2- and 4-chloropyridines undergo nucleophilic aromatic substitution to give the corresponding ethoxypyridine, whereas 3-chloropyridine does not.

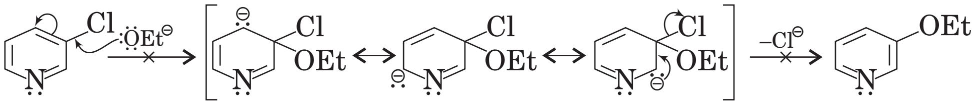


2-Chloropyridine

(especially stable)

Intermediate (more stable)

2-Ethoxypyridine



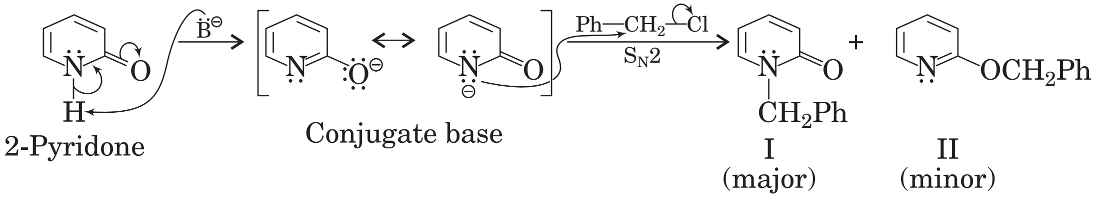
3-Chloropyridine

Intermediate (less stable)

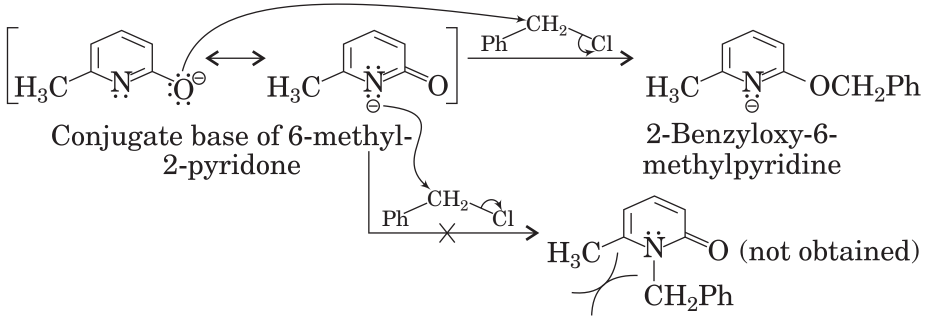
3-Ethoxypyridine

(c) The conjugate base of 2-pyridone is, in fact, an ambident nucleophile. It may react with benzyl chloride ($PhCH_2Cl$) to give the *O*-alkylation product 2-benzyloxypyridine (II) as well as the *N*-alkylation product *N*-benzyl-2-pyridone

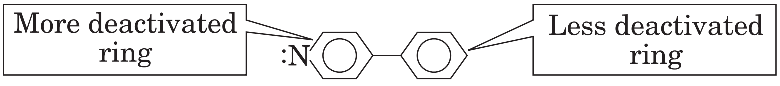
(I). Since it is an S_N2 reaction, nucleophilic attack on $PhCH_2Cl$ occurs preferably through the less electronegative and more polarizable, i.e., more nucleophilic N atom to yield *N*-benzyl-2-pyridone as the major product.



In the ambident anion obtained from 6-methyl-2-pyridone, the CH_3-group at C-6 sterically hinders the approach of the soft centre (i.e., N) of the anion towards $PhCH_2Cl$ and for this reason, *O*-alkylation takes place preferentially to give 2-benzyloxy-6-methylpyridine as the major product.


H₃C
Ph
CH₂
Cl
OCH₂Ph
Conjugate base of 6-methyl-2-pyridone
2-Benzyloxy-6-methylpyridine
CH₂Ph
(not obtained)

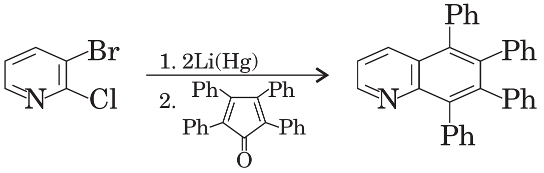
(d) Due to electron withdrawal by ring nitrogen, the pyridine ring is deactivated towards electrophilic aromatic substitution. For this reason, the electrophilic substitution preferably takes place at the benzene ring.



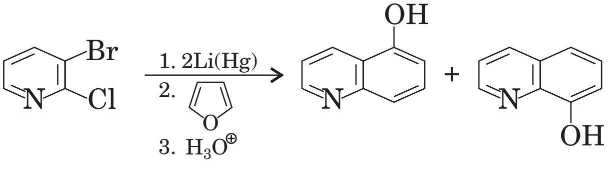
4-Phenylpyridine

11. Give an arrow-formalism mechanism for each of the following reactions:

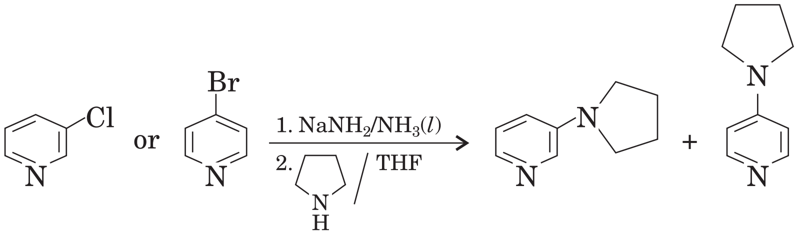
(a)



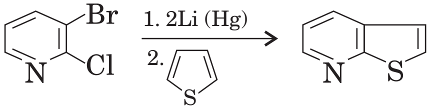
(b)



(c)

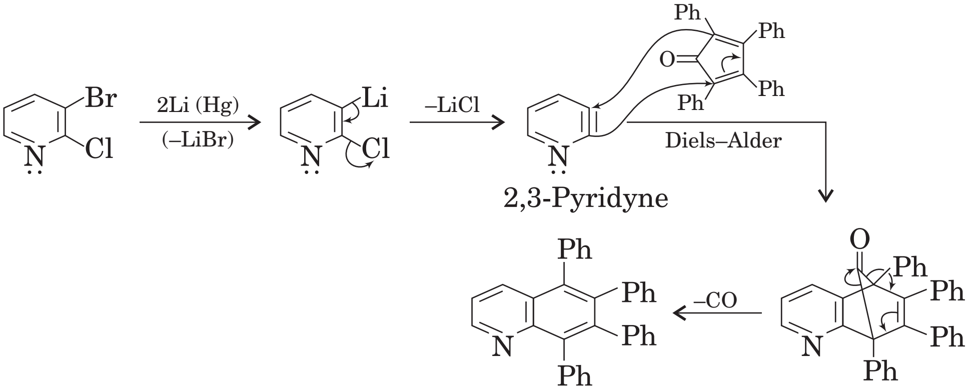


(d)

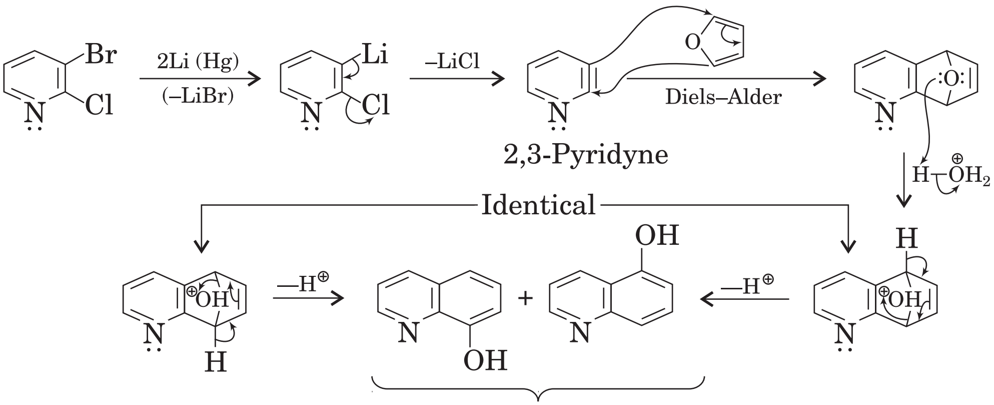


Solution

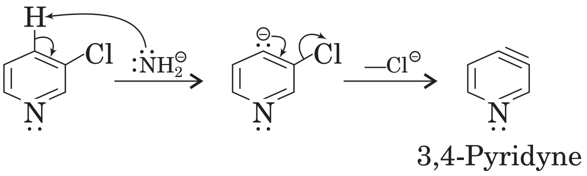
(a)

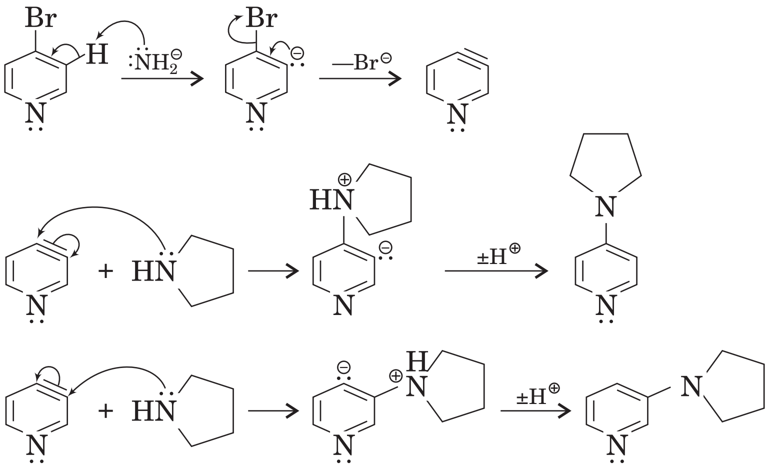


(b)

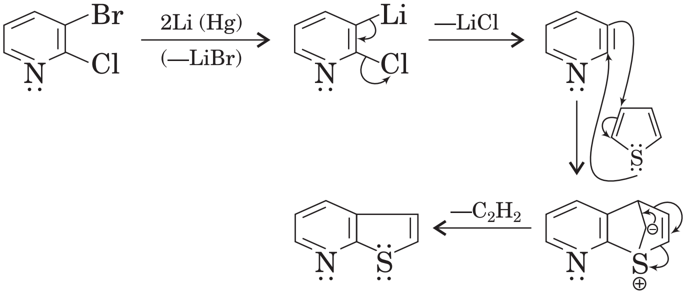


(c)





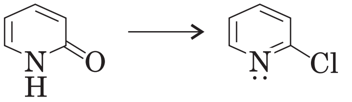
(d)



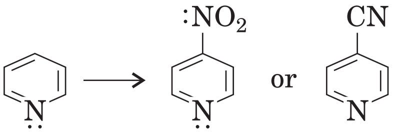
With thiophine, 2,3-pyridyne undergoes a (3 + 2) cycloaddition involving the sulphur atom and the β-carbon of thiophene. The intermediate adduct loses acetylene to produce pyridothiophene.

12. How would you carry out the following transformations?

(a)

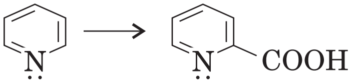


(b)



[C.U. 2010, 2011]

(c)



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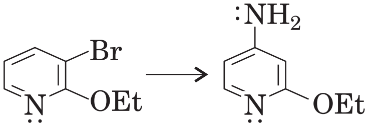

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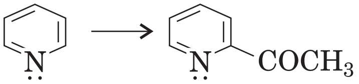

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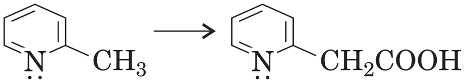
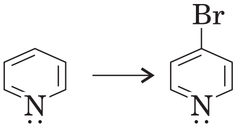


(g)



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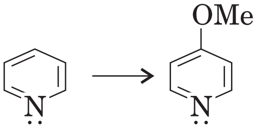
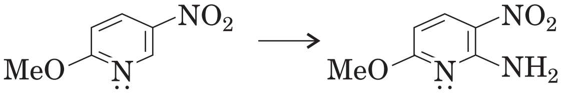
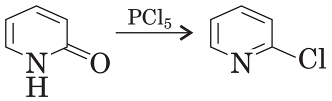


(i)

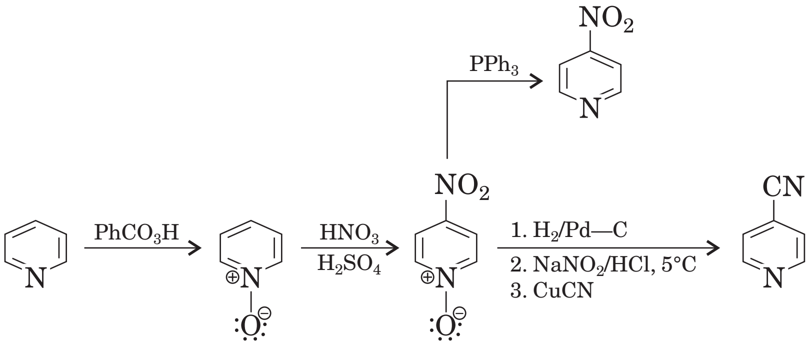


Solution

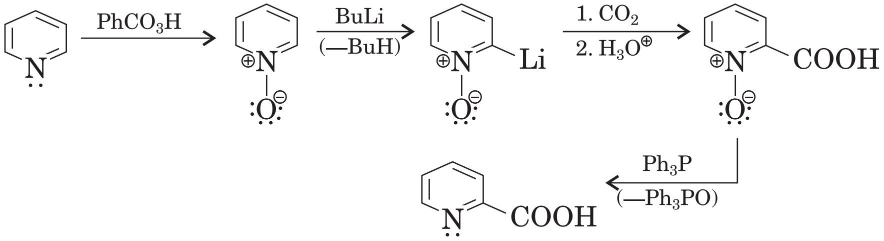
(a)



(b)



(c)



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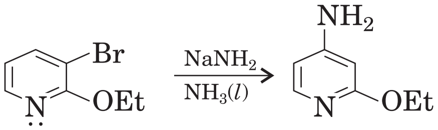

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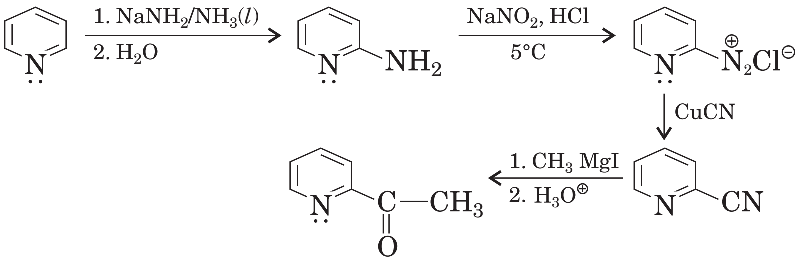

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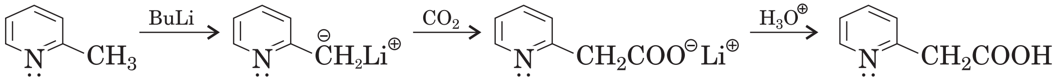

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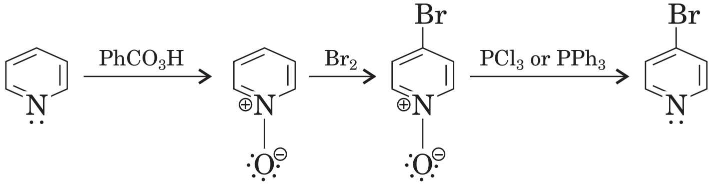

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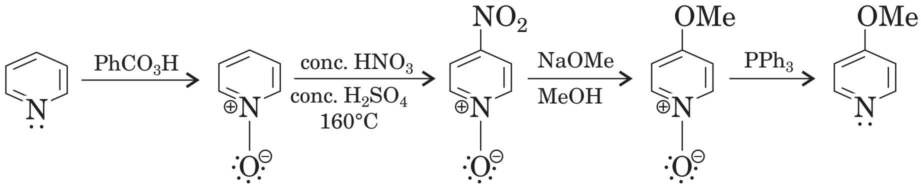
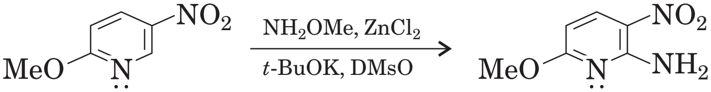
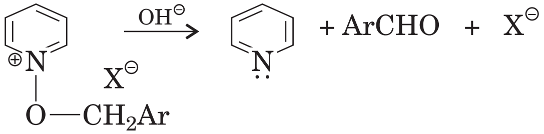


(i)

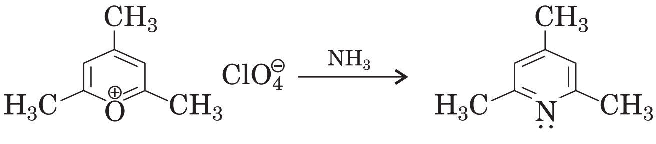


13. Provide a reasonable mechanism for each of the following reactions:

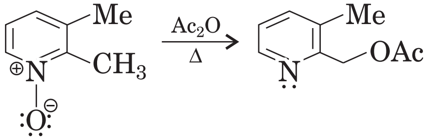
(a)



(b)

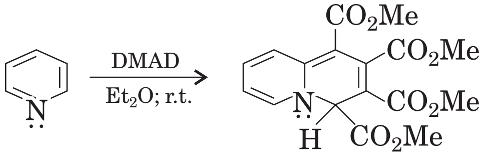


(c)



[C.U. 2012]

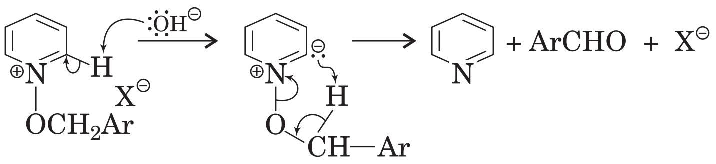
(d)



[C.U. 2011]

Solution

(a)



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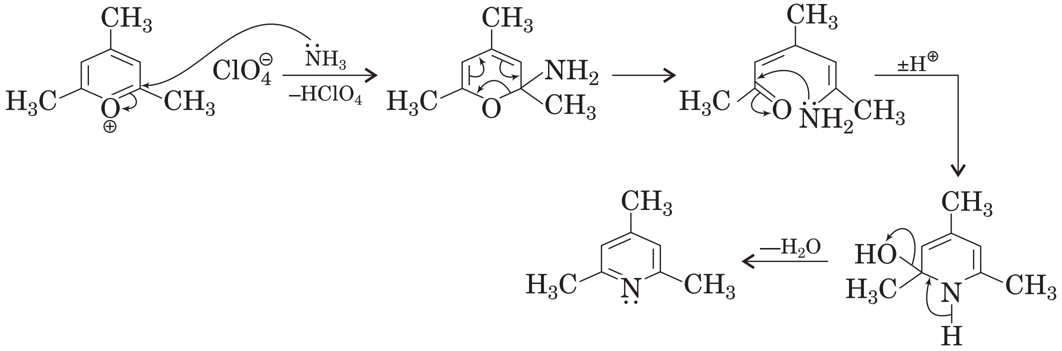

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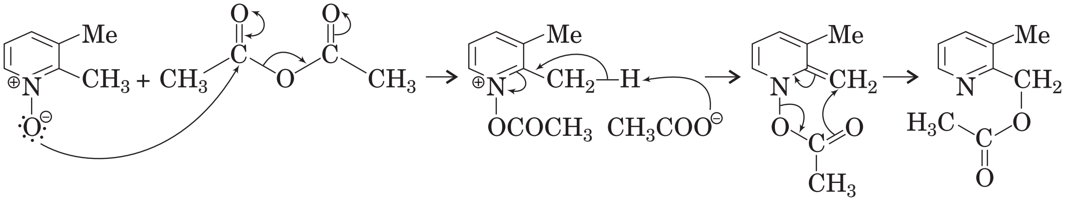

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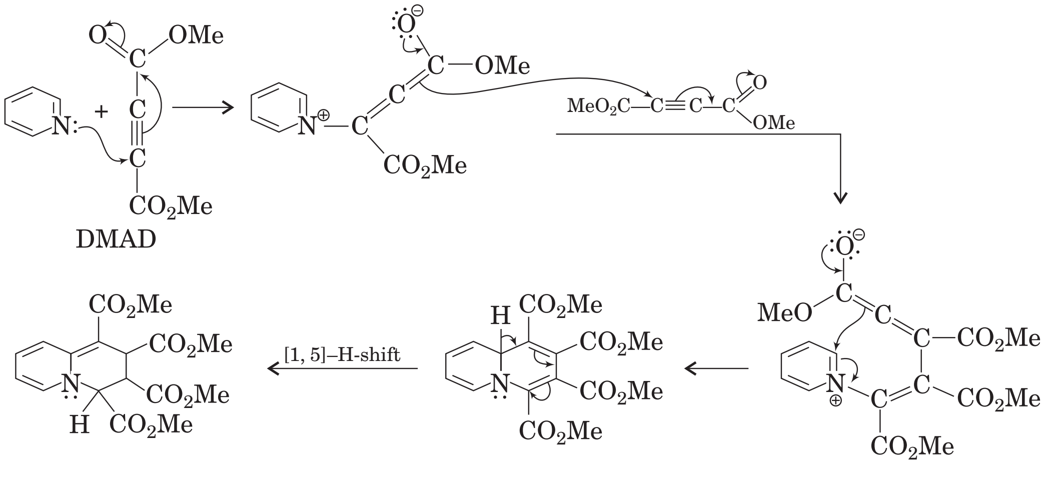
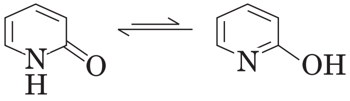
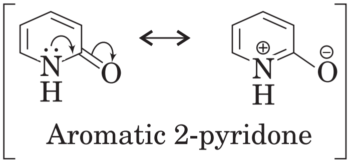


14. In the following, the equilibrium lies to the left—Explain.

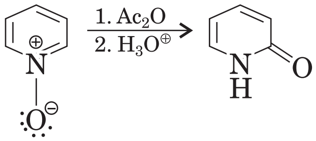


Solution 2-Hydroxypyridine prefers to exist as the amide because that has the advantage of a strong C═O bond and is still aromatic. There are two electrons in each of the C═C bonds and two also on the trigonal N atom of the amide. If becomes clear from the delocalization of the lone pair of typical amide style.

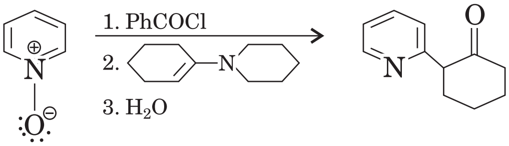


15. Provide an arrow pushing mechanism for each of the following reactions:

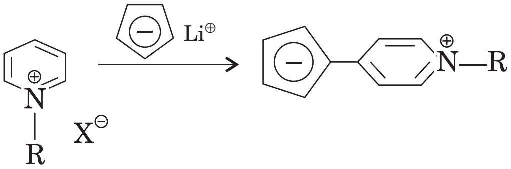
(a)



(b)



(c)



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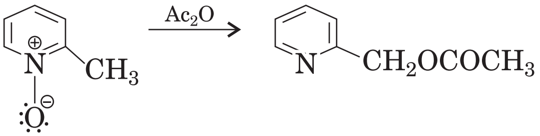

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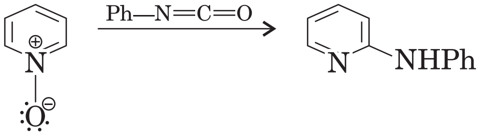

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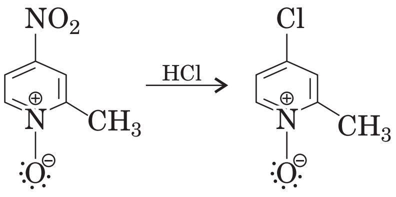
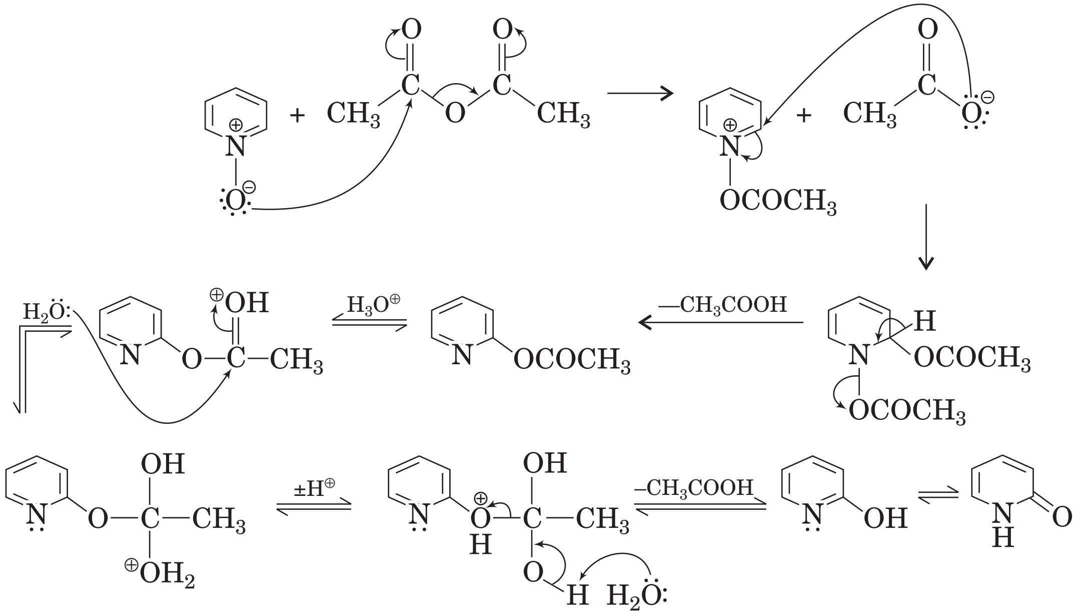
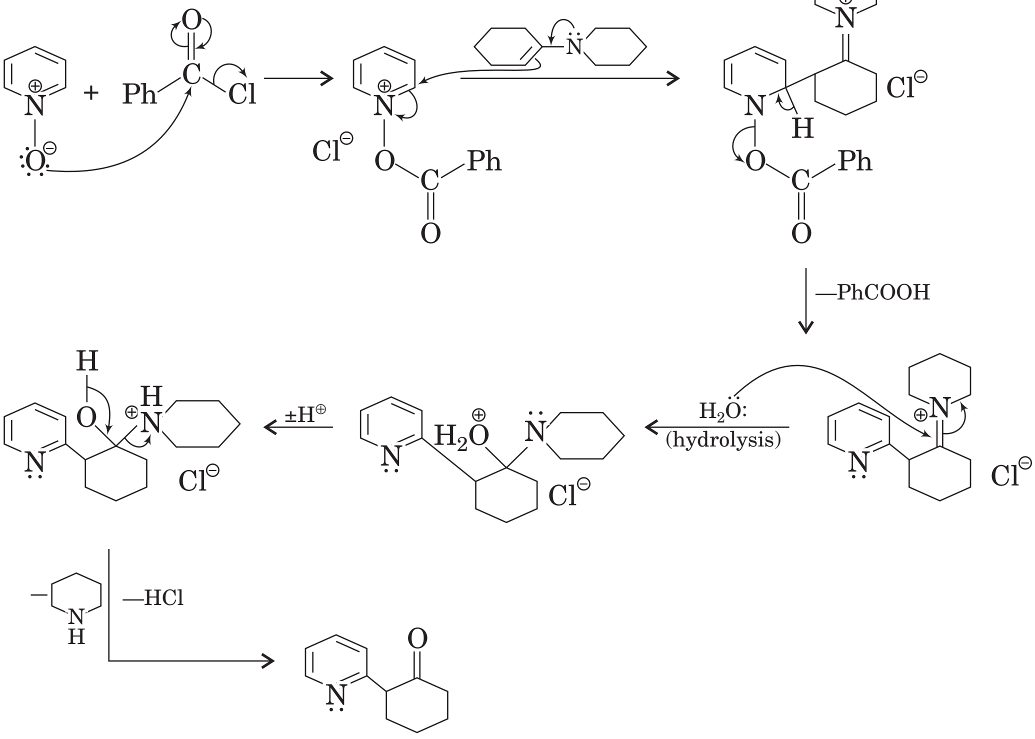


Solution

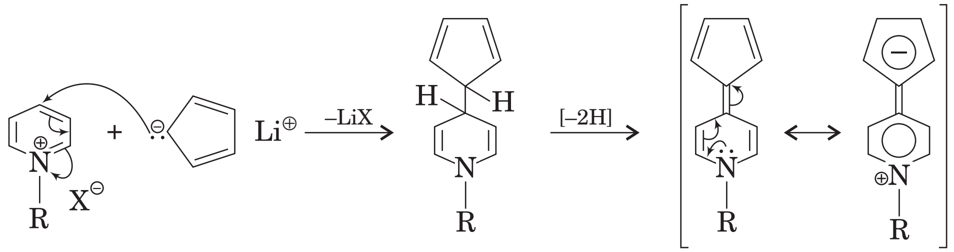
(a)


+
CH_3
$H_3O^{\oplus}$
—CH_3COOH
$H_2\ddot{O}$:
±$H^{\oplus}$
$-CH_3COOH$
$OCOCH_3$

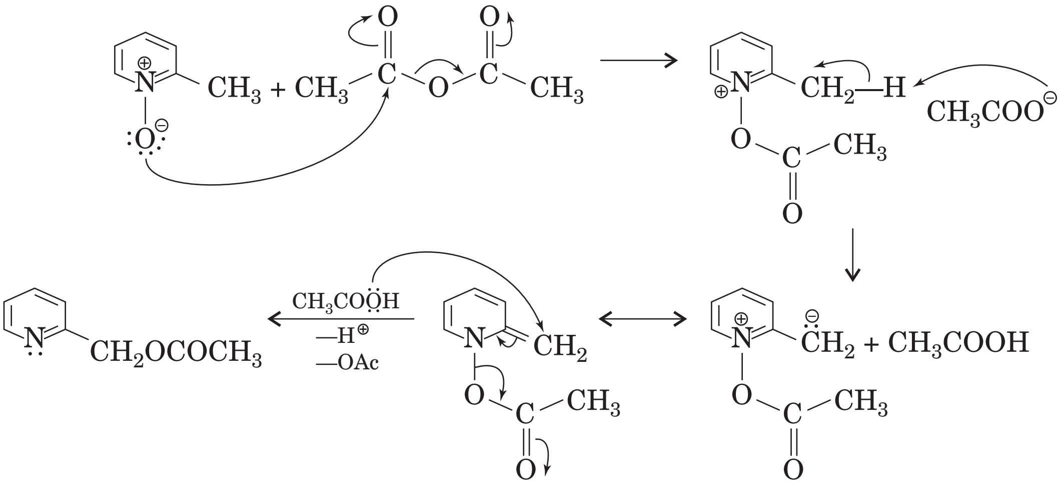
(b)


+
Ph
Cl
$Cl^{\ominus}$
—PhCOOH
$H_2\ddot{O}$:
(hydrolysis)
±$H^{\oplus}$
—HCl

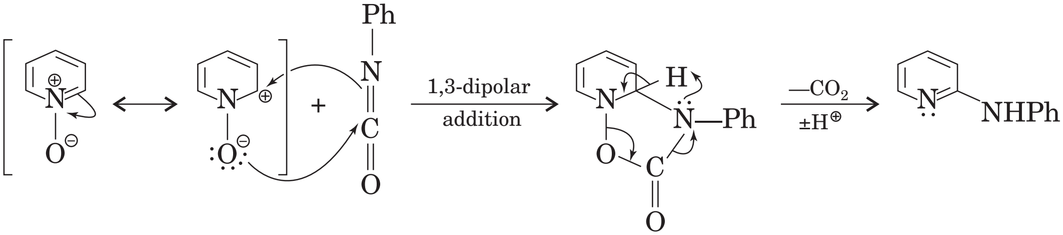
(c) Cyclopentadienyl anion reacts with the pyridinium salt to give mainly 1,4-dihydropyridine, which readily undergo dehydrogenation to an aromatic zwitterionic species.



(d)



(e)



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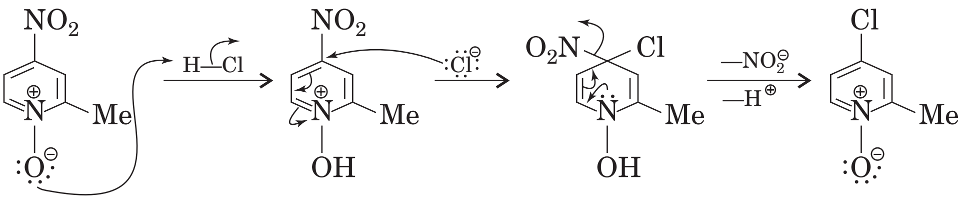
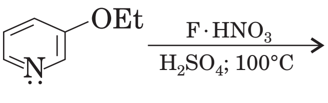
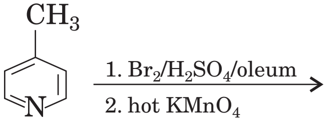


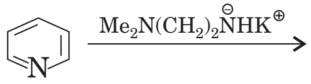
16. Draw the structure of the product:

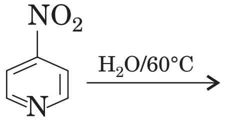
(a)

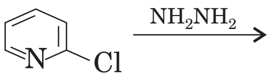


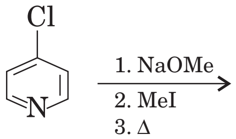
(b)

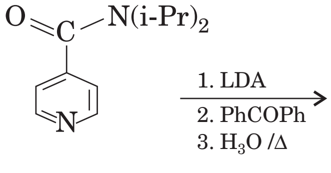


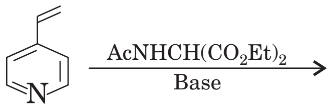
(c) 

(d) 

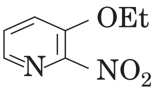
(e) 

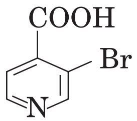
(f) 

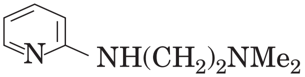
(g) 

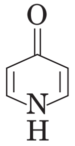
(h) 

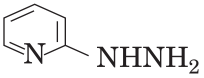
Solution

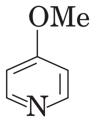
(a) 

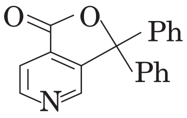
(b) 

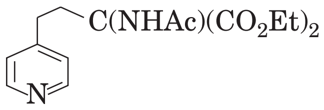
(c) 

(d) 

(e) 

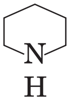
(f) 

(g) 

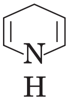
(h) 

17. Provide structures of the products obtained when pyridine is reduced with (a) Na/EtOH or H_2/Ni, (b) Na/NH_3(l) and EtOH (Birch reduction), (c) $LiAlH_4$/ether, and (iv) HI/300°C.

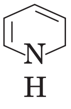
Solution

(a) 

(Piperidine)

(b) 

(1,4-Dihydropyridine)

(c) 

(1,2-Dihydropyridine)

(ring-opening reduction)

(d) Pentane ($CH_2CH_2CH_2CH_2CH_3$) + NH_3

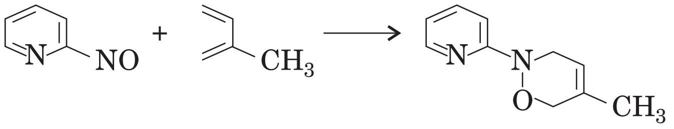
18. How can you synthesize 2,4,6-trimethylpyridine using suitable starting materials. [C.U. 2013, 2015]

Solution See **article no. 6.3.1.1** (Hantzsch synthesis).

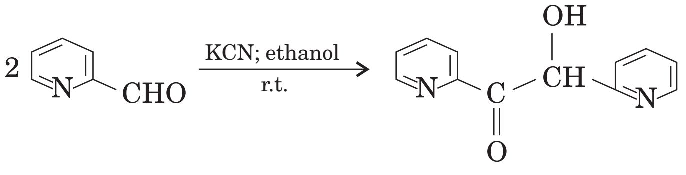
STUDY PROBLEMS

1. Offer explanation for the following observations:
   (a) Bromine atom in 3-bromopyridine but not in bromobenzene can be replaced by sodium methoxide in methanol.
   (b) 4-Chloro-3-nitropyridine hydrolyzes readily even in warm water.
   (c) Nitration for pyridine *N*-oxide occurs at 4-position while sulphonation at 3-position though both are carried out in the presence of H_2SO_4.
   (d) Pyridine is miscible with water but pyrrole is only slightly soluble.
   (e) Pyridine is less basic than imidazole.
   (f) Quinuclidine is more basic than pyridine.
   (g) 2,6-Dimethylpyridine is less reactive than pyridine towards BMe_3.
2. Discuss the behaviour of the three picolines in aqueous NaOH containing D_2O. **[C.U. 2014]**
   [**Hint:** See **solved Problem 10(a)**. Methyl hydrogens of 2- and 4- picolines will be substituted by D.]
3. Predict the relative reactivities of bromobenzene, 2-bromopyridine, 3-bromopyridine towards replacement of the halide with ethoxide ion on treatment with sodium ethoxide.
4. What factors make it very difficult to bring about electrophilic substitution of pyridine than benzene?
5. In pyridine *N*-oxides, both electrophilic and nucleophilic substitutions of halide from C-4 take place rapidly than in pyridine. Explain.
6. Predict the product expected to be formed when a 1:1 mixture of 2- and 3-methylpyridines is treated with LDA (0.5 equiv.) followed by MeI (0.5 equiv.)
7. 2-Aminopyridine can be nitrated or sulphonated under much milder conditions than pyridine itself and substitution occurs chiefly at the 5-position. Account for these observations.
8. Suggest a mechanism for each of the following reactions:

(a)



(b)



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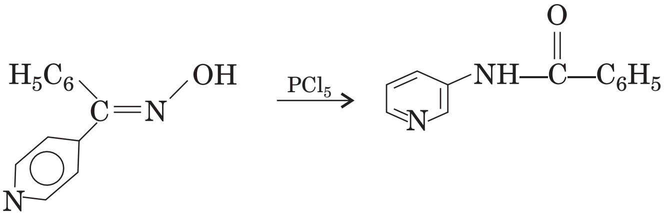
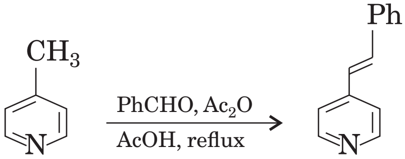
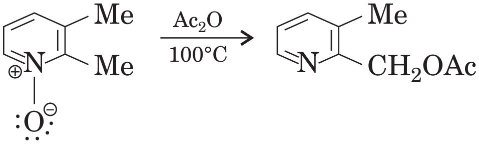


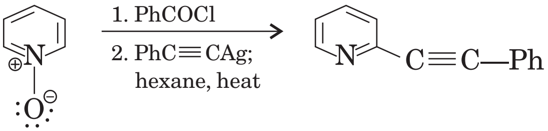
(d)



(e)



(f)

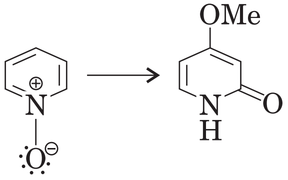


9. When pyridine *N*-oxide is heated with a mixture of conc. HNO_3 and conc. H_2SO_4, a product $C_5H_4N_2O_3$ is obtained. When this compound is treated with PCl_3 and then H_2/Pd-C, $C_5H_4N_2O_3$ and $C_5H_6N_2$ are respectively obtained. Identify these three products.

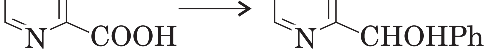
10. Nitration of 2- and 4-aminopyridines can be achieved easily, even though nitration of aniline is not generally possible. Explain.

11. How would you carry out the following transformations?

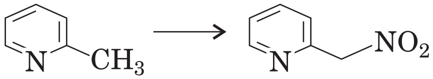
(a)



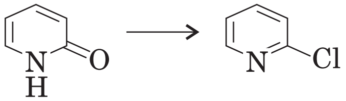
(b)



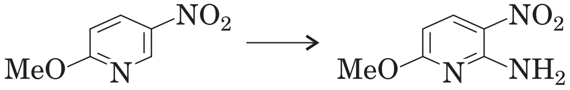
(c)

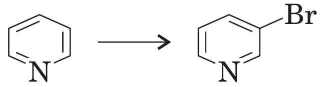


(d)

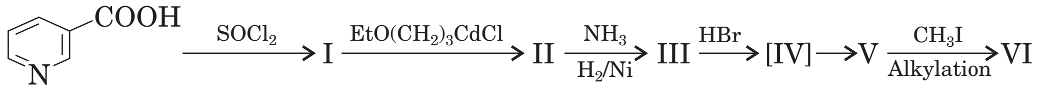


(e)



(f) 

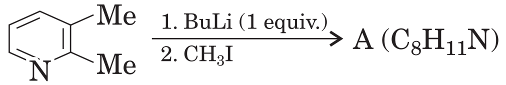
12. Provide structures for the compounds I–VI. The compound VI is an alkaloid, the leavorotatory form of which is present in tobacco. Write its name.

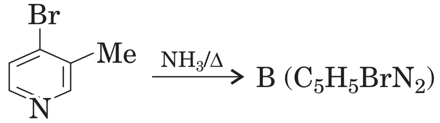


13. Outline a synthesis for each of the following pyridine derivatives from the indicated starting material and any other reagents.

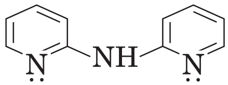
(a) 3-Methyl-4-nitropyridine from 3-methylpyridine
(b) 4-Methyl-3-nitropyridine from 4-methylpyridine
(c) 2-Pyridineacetic acid from 2-methylpyridine
(d) 3-Aminopyridine from 3-methylpyridine

14. Predict the major product in each of the following reactions. Give your reasoning.

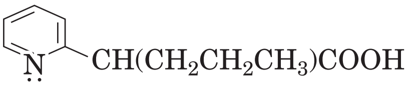
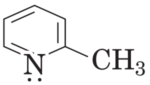
(a) 

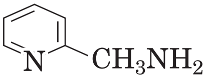
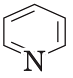
(b) 

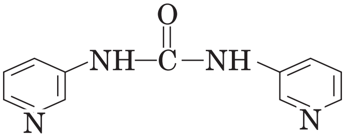
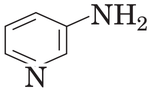
15. The following amine is isolated as a by-product in the Chichibabin reaction of pyridine and $NaNH_2$. Provide a reasonable mechanism for its formation.

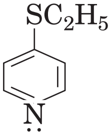
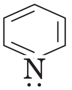


16. Outline a synthesis for each of the following compounds from the indicated starting material and any other necessary reagents:

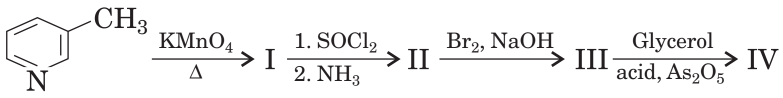
(a)  from 

(b)  from 

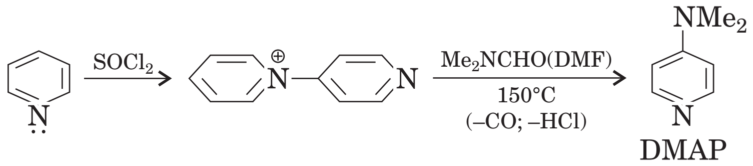
(c)  from 

(d)  from 

17. Identify compounds I–IV in the following reaction sequence:



18. The synthesis of DMAP (a useful acylation catalyst) is carried out by initial attack of thionyl chloride on pyridine. Suggest a mechanism for each step of the following reaction sequence:

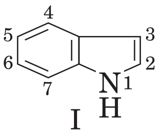


19. Explain with examples the close similarity of (a) pyridine with nitrobenzene, (b) α-picoline with *o*-nitrotoluene, (c) pyrrole with phenol, (d) furfural with benzaldehyde and (e) thiophene with benzene.

6.4 BENZO-FUSED FIVE- AND SIX-MEMBERED HETEROCYCLIC COMPOUNDS WITH ONE HETEROATOM

6.4.1 Indole and Its Derivatives

The indole (I) ring comprises a benzene ring fused to the 2- and 3-positions. The atoms are numbered as shown commencing from the nitrogen atom and going anti-clockwise around the two condensed rings. Positions 2- and 3- are also sometimes designated as α and β respectively.

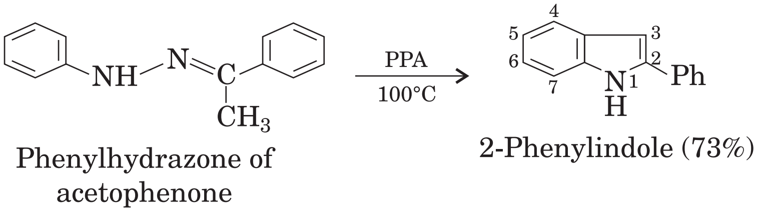


I

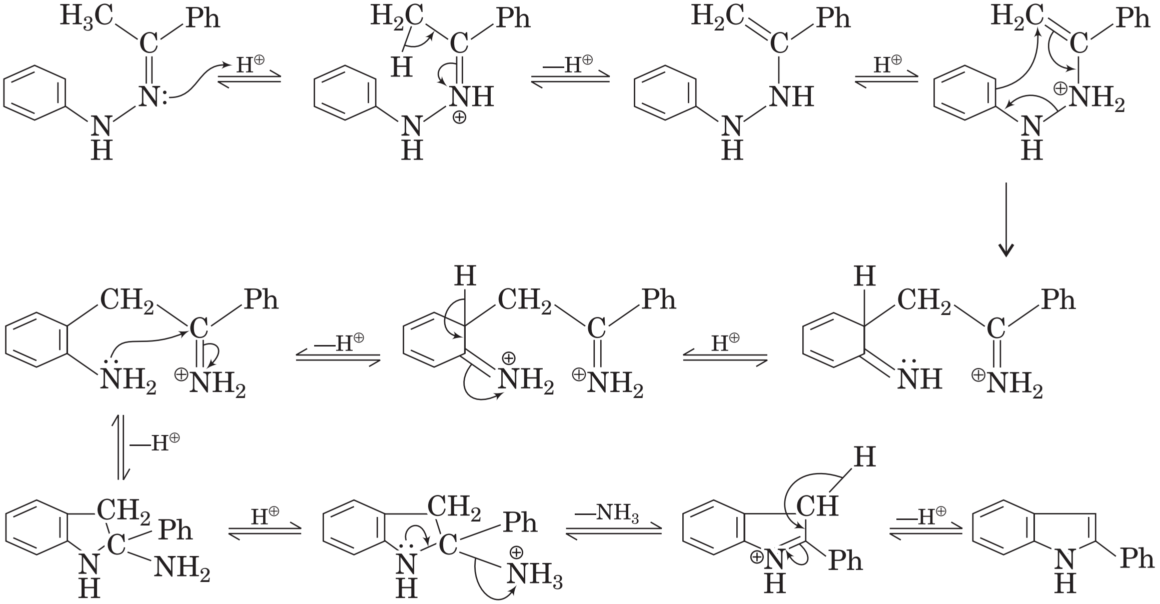
Indole was first prepared by Baeyer in 1866 by zinc dust distillation of oxindole. Indole and its derivatives occupy a special place in chemistry because of their wide occurrence in many natural products. When the naturally occurring dye indigo is chemically degraded, indole is obtained finally. It is also found in coal tar, in essential oils like jasmine oil and orange oil, in the amino acid tryptophan and in alkaloids like brucine and psilecene.

6.4.1.1 Synthetic Methods

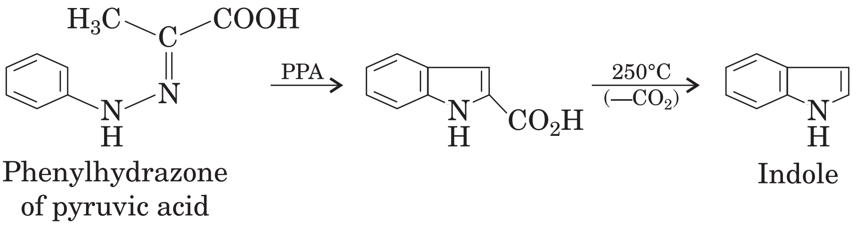
1. The Fischer Indole Synthesis This is one of the best-known methods for preparing indoles in which the phenylhydrazone of an aldehyde or ketone is treated with Lewis acid catalyst like BF_3 or $ZnCl_2$ or a proton acid catalyst like H_2SO_4 or polyphosphoric acid (PPA, a syrupy mixture of P_2O_5 and H_3PO_4). The aldehyde or ketone may also be treated directly with phenylhydrazine in the presence of acid catalyst. When the phenylhydrazone of acetophenone ($PhCOCH_3$), for example, is treated with PPA, 2-Phenylindole is obtained.



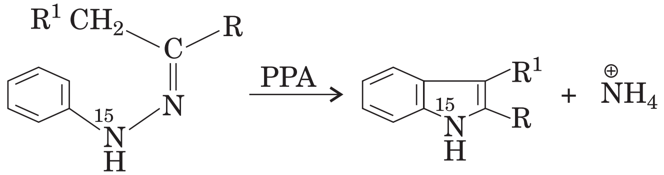
Mechanism of the reaction The reaction occurs by the following mechanism which involves a [3,3] sigmatropic (*o*-Claisen type) rearrangement of the protonated tautomer of the hydrazone with subsequent loss of a molecule of ammonia.



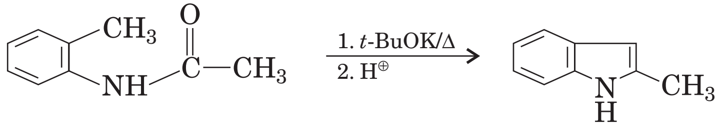
The reaction cannot be used to prepare indole itself by using acetaldehyde. However, indole can be prepared by using the phenylhydrazone of pyruvic acid followed by decarboxylation of the resulting indole-2-carboxylic acid.



Evidence for the mechanism The mechanism of reaction has been proved by a labelling experiment. When the reaction is carried out with ^{15}N-labelled hydrazones, it is found that the nitrogen atom farther from the ring is eliminated as ammonia.



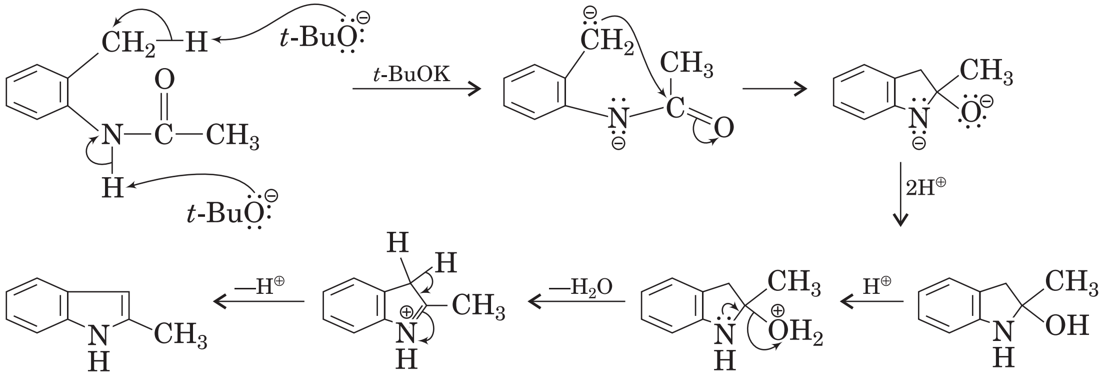
2. The Madelung Synthesis This method involves cyclodehydration of a 2-acylaminotoluene in the presence of a strong base such as potassium *t*-tuboxide, sodamide, etc. For example:



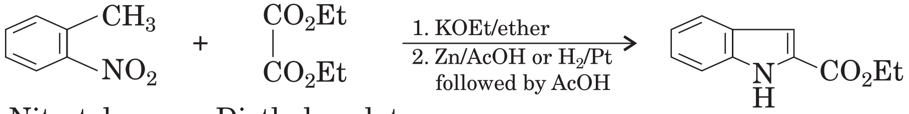
2-Acetylaminotoluene 2-Methylindole

Indole itself can be prepared by using *o*-formamidotoluene.

Mechanism of the reaction

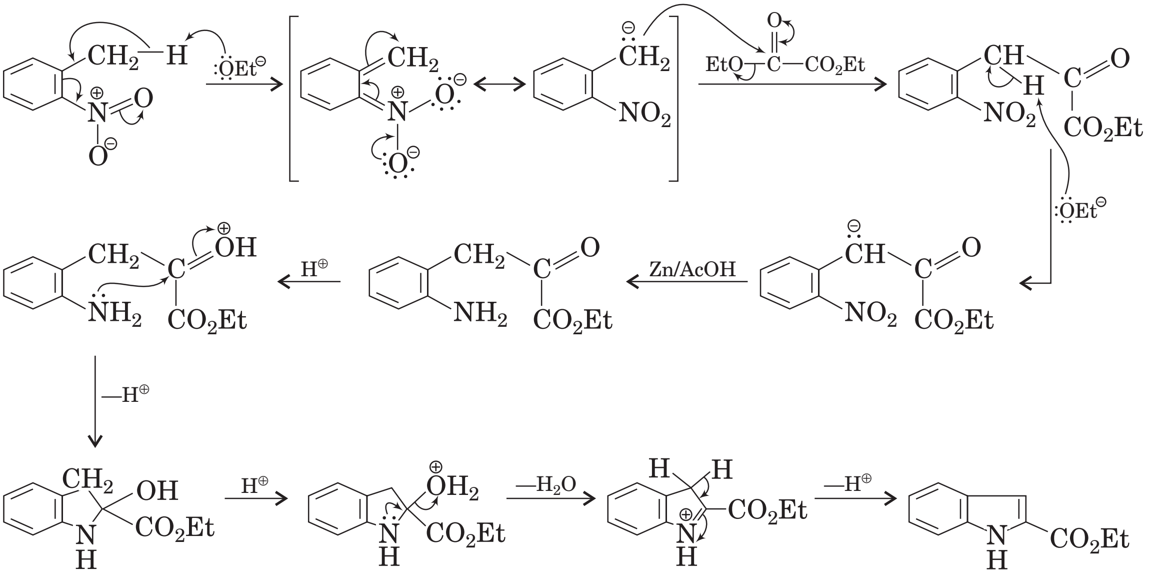


3. The Reissert Synthesis This is a convenient method for the synthesis of indole and its derivatives. It involves a base-catalyzed condensation of *o*-nitrotoluene or a substituted derivative with diethyl oxalate in the pressure of potassium or sodium ethoxide in dry ether solvent. The resulting *o*-nitrophenylpyruvate undergoes reductive cyclization to yield an indole derivative when treated with Zn/AcOH or H_2/Pt followed by AcOH. For example:

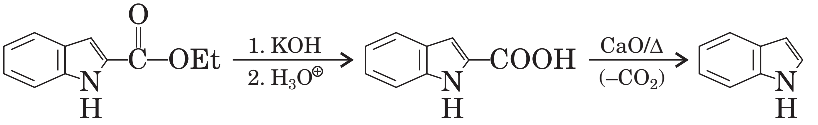


o-Nitrotoluene Diethyl oxalate Ethyl 2-indolecarboxylate (65%)

Mechanism of the reaction Base abstracts a benzylic hydrogen (acidic enough due to presence of the —NO_2 group) to form a resonance-stabilized carbanion. The anion attacks a carbonyl group of diethyl oxalate, displacing ethanol. Like the Claisen condensation this reaction is driven to completion by ionization of the product. The nitro-group is then reduced to an amino group, which subsequently reacts with the neighbouring ketone to yield the aromatic indole.

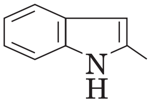


The resulting compound can be converted to indole as follows:



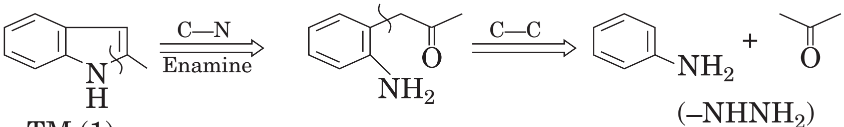
Indole

Synthesis of Some Indole Derivatives (Target Molecules) through Disconnection Approach

1.  (2-Methylindole)

TM (1)

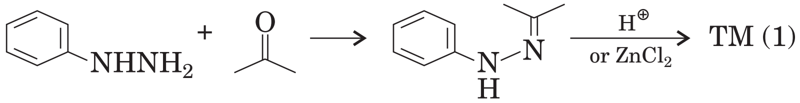
Retrosynthetic analysis (I)



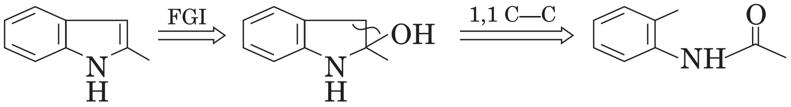
TM (1)

The ‘obvious’ C—N disconnection followed by C—C disconnection gives rise to starting materials of what is called *Fischer indole synthesis* in which the phenylhydrazone of a ketone is treated with acid (or Lewis acid $ZnCl_2$).

Synthesis (I)



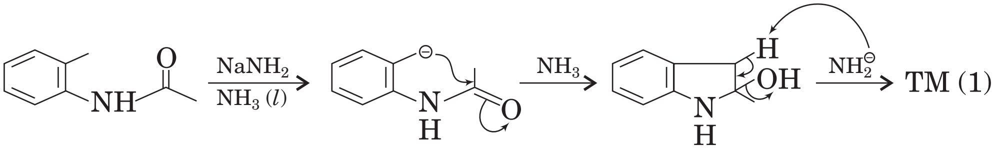
Retrosynthetic analysis (II)

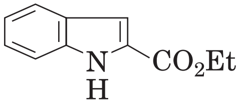


TM (1)

When an acylamidotoluene is treated with a strong base (NaNH$_2$ or *t*-BuOK), an indole is obtained (the *Madelung synthesis*).

Synthesis (II)

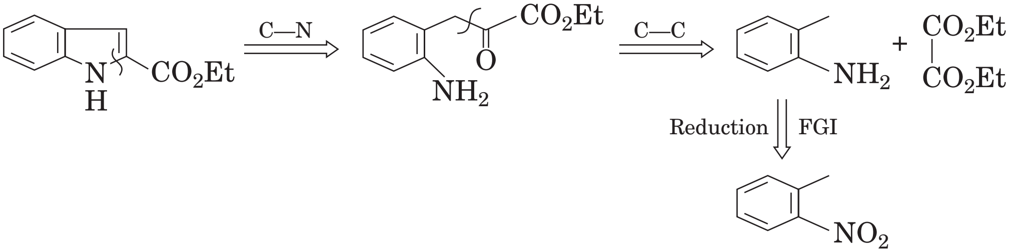


2. 

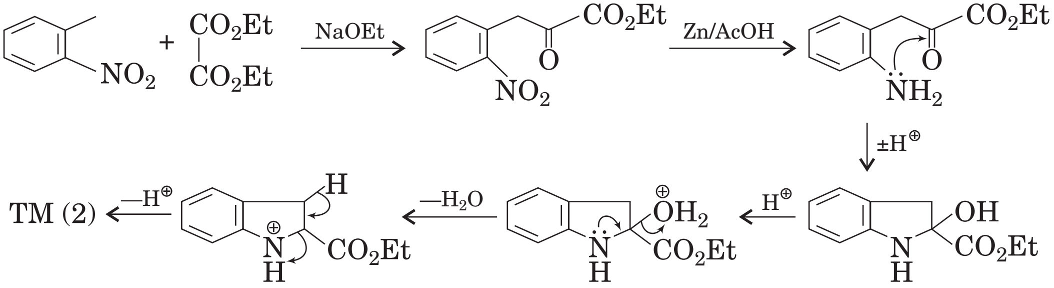
(Ethyl 2-indolecarboxylate)

TM (2)

Retrosynthetic analysis

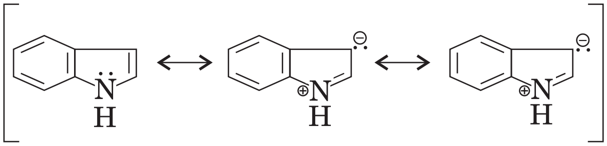


Synthesis



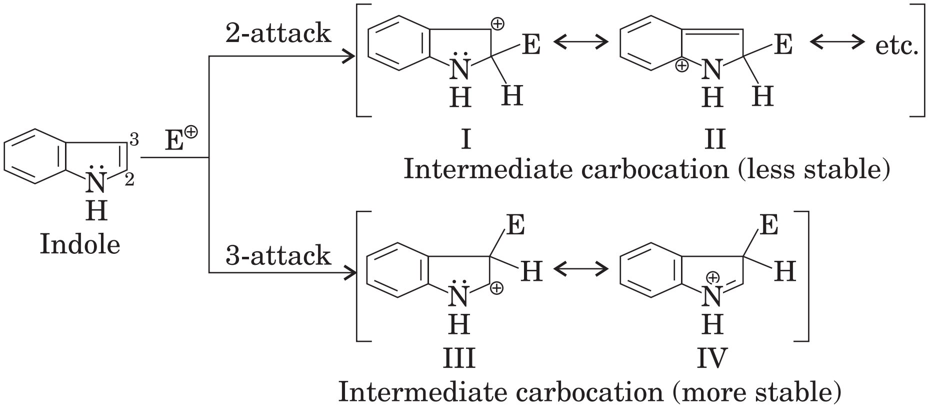
6.4.1.2 Properties and Reactions

Indole is a colourless crystalline solid having m.p. 52°C. It resembles pyrrole, in general, chemical reactions; however, it differs from the latter in many ways due to presence of a benzene ring. Indole is a planar conjugated system of 10 π-electrons, 2 from the nitrogen and 8 from the carbon atoms and is thus a π-excessive molecule. Its resonance energy has been found to be 47–49 kcal/mol. From the valence-bond point of view, indole is a resonance hybrid of three principal resonance structures.



Presence of high electron density at the 3-position has been supported by the calculation of π-electron densities and by the molecular orbital methods. Indole like pyrrole is a very weak base.

1. Electrophilic substitution Indole undergoes electrophilic substitution predominantly at position-3. Due to fusion of a benzene ring, the position of greatest electron density of the pyrrole ring is changed from position-2 to position-3. Electrophilic attack at the 2-position of indole yields an intermediate carbocation that is a hybrid of structure I in which the positive charge is accommodated by the heterocyclic ring, and several other structures like II in which the charge is accommodated by the benzene ring. On the other hand, attack at 3-position yields on intermediate carbocation that is a hybrid of structure III and IV in which the positive charge is accommodated by the heterocyclic ring. In structures I, III and IV, the aromatic sextet is preserved in the benzene ring. On the other hand, in structures like II, the aromatic sextet is disrupted in both the rings, with a large sacrifice of resonance stabilization. Structures like I, II and IV are much more stable. However, there are two stable contributing structures (III and IV) for attack at the 3-position and only one (I) for attack at the 2-position. The structure IV is especially stable because all atoms have complete octets. The carbocation resulting from attack at 3-position (and the transition state leading to that ion) is, therefore, expected to be much more stable than the carbocation (and the corresponding T.S.) resulting from attack at the 2-position and the electrophilic substitution is expected to take place much more rapidly and predominantly at the 3-position.



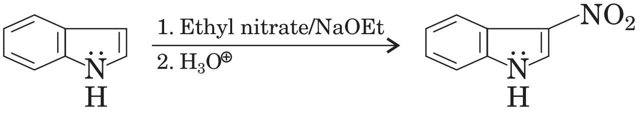
Intermediate carbocation (less stable)

Intermediate carbocation (more stable)

If the position-3 of indole is occupied, then 2-substitution occurs. If both the 2- and 3-positions are blocked, then the benzene ring is attacked at the 6-position.

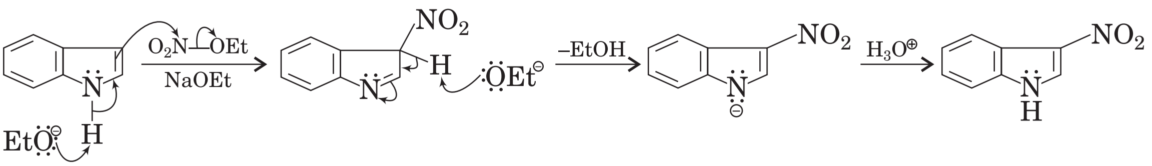
Some electrophilic substitution reactions of indole are given below:

(i) Nitration When a mixture of indole and sodium ethoxide with ethyl nitrate, 3-nitroindole is obtained.

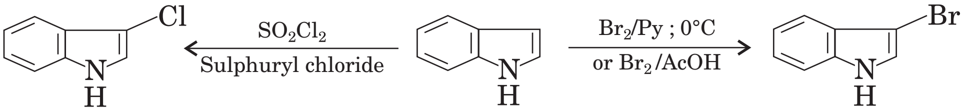


3-Nitroindole

Mechanism

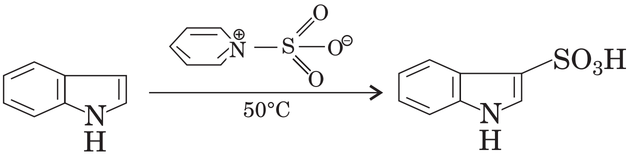


(ii) Halogenation



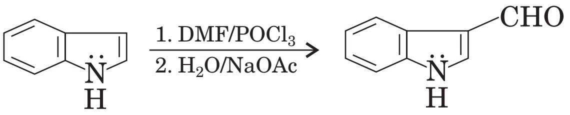
3-Chloroindole 3-Bromoindole

(iii) Sulphonation Sulphonation of indole is carried out only under milder conditions using pyridine–sulphur trioxide complex in order to reduce problems associated with acidity.



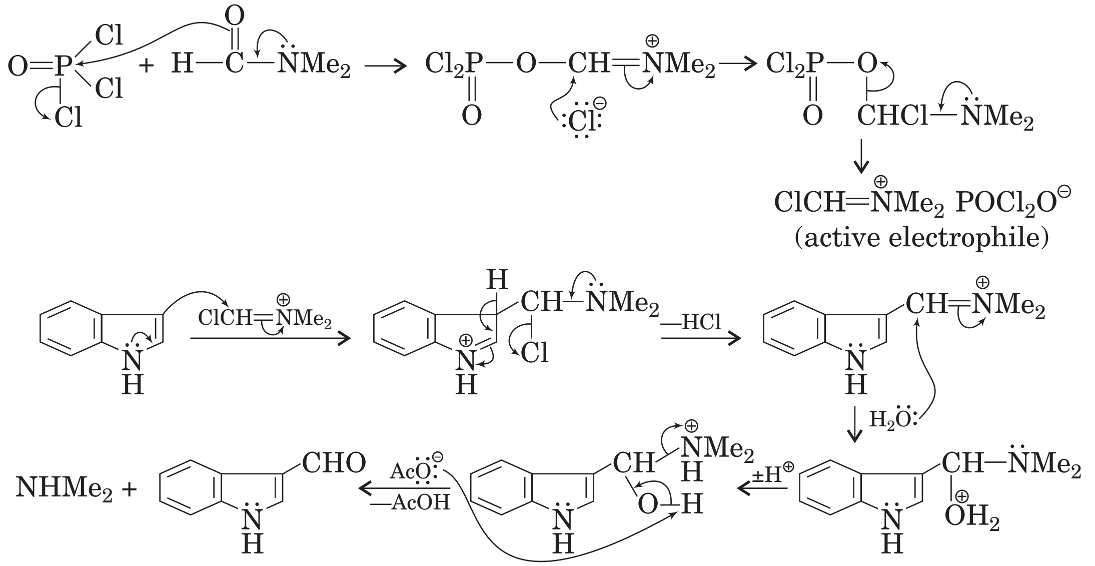
3-Indolesulphonic acid

(iv) Vilsmeier–Haack reaction β-Formylation of indole can be carried out smoothly by this reaction.



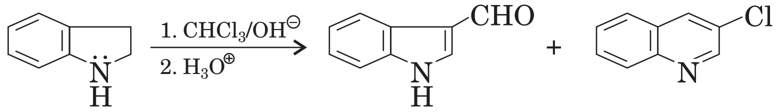
3-Formylindole

Mechanism of the reaction



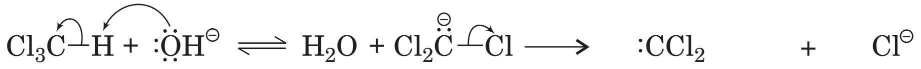
3-Formylindole

(v) Reimer–Tiemann reaction Indole reacts with $CHCl_3/OH^{\ominus}$ to yield, after acidification, a mixture of 3-formylindole and 3-chloroquinoline.



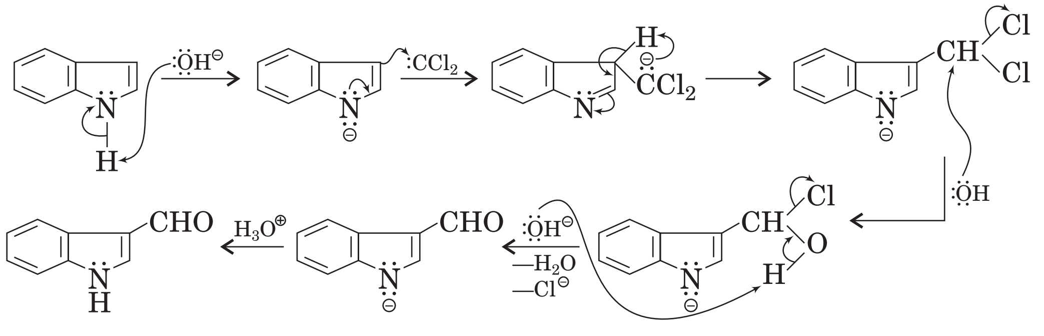
Indole 3-Formylindole 3-Chloroquinoline

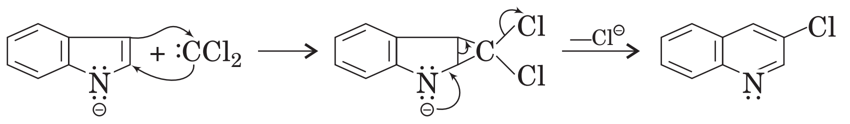
Mechanism of the reaction



$$Cl_3C{-}H + :\ddot{O}H^{\ominus} \rightleftharpoons H_2O + Cl_2\overset{\ominus}{C}{-}Cl \longrightarrow :CCl_2 + Cl^{\ominus}$$

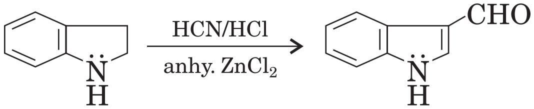
Dichlorocarbene (electrophile)





3-Chloroquinoline

(vi) Gattermann reaction β-formylation of indole may also be carried out by the Gattermann reaction.

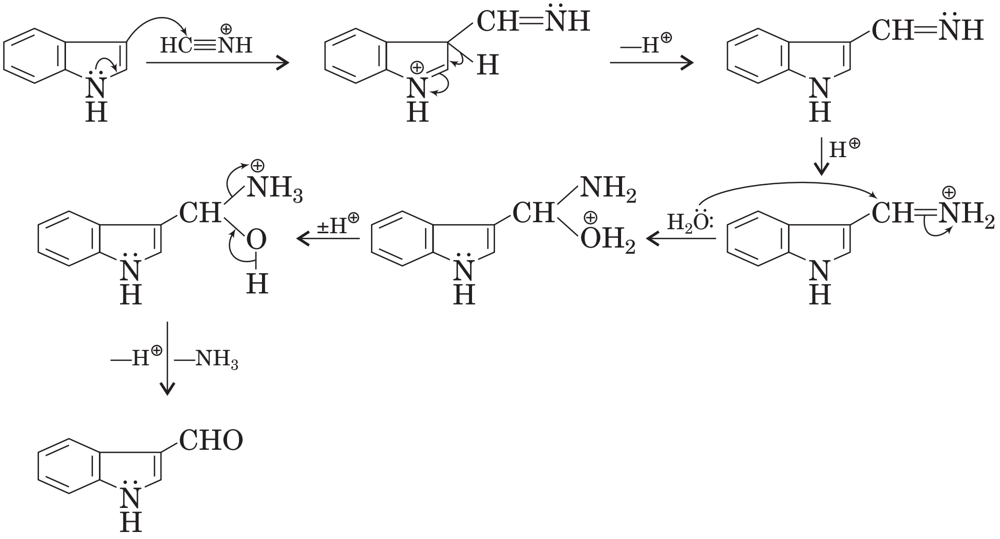


Indole 3-Formylindole

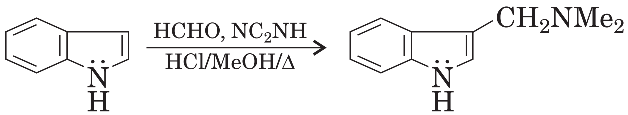
Mechanism of the reaction

$$ZnCl_2 + 2HCl \rightleftharpoons 2H^{\oplus}ZnCl_4^{2\ominus}$$

$$2H-C\equiv N + 2H^{\oplus}ZnCl_4^{2\ominus} \rightleftharpoons 2[H-C\equiv\overset{\oplus}{N}H \leftrightarrow H-\overset{\oplus}{C}=NH] + ZnCl_2^{2\ominus}$$

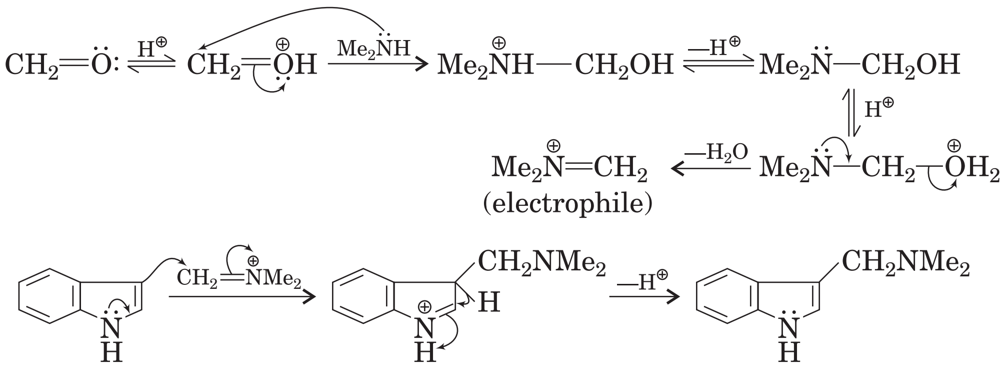

HC≡$\overset{\oplus}{N}$H
CH=N̈H
H
—H$^{\oplus}$
CH=N̈H
H$^{\oplus}$
CH=$\overset{\oplus}{N}$H$_2$
H$_2$Ö:
CH
NH$_2$
$\overset{\oplus}{O}$H$_2$
±H$^{\oplus}$
CH
$\overset{\oplus}{N}$H$_3$
O
H
—H$^{\oplus}$ —NH$_3$
CHO

(vii) Mannich reaction Indole reacts with formaldehyde and dimethylamine in acid solution to yield gramine (3-dimethylaminomethylindole).

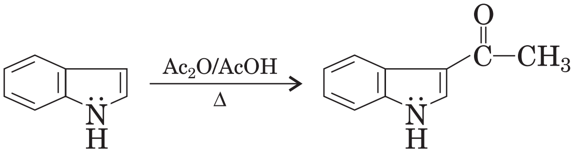


3-Dimethylaminomethylindole

Mechanism of the reaction

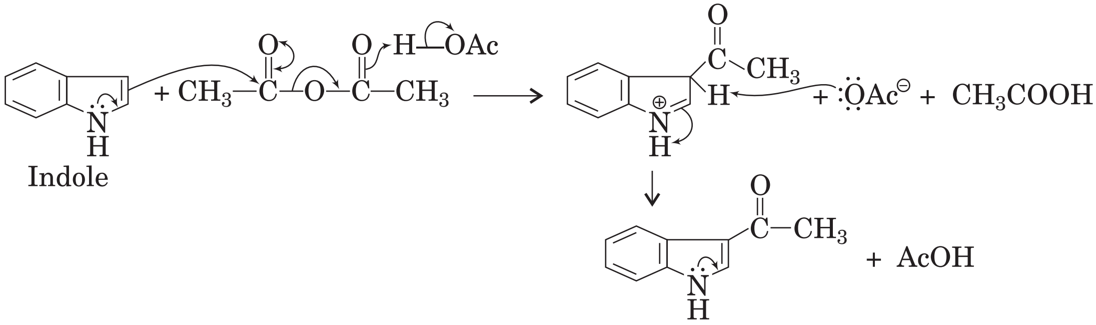

$CH_2{=}\ddot{O}:$
$H^{\oplus}$
$CH_2{=}\overset{\oplus}{O}H$
$Me_2\ddot{N}H$
$Me_2\overset{\oplus}{N}H{-}CH_2OH$
$-H^{\oplus}$
$Me_2\ddot{N}{-}CH_2OH$
$H^{\oplus}$
$Me_2\ddot{N}{-}CH_2{-}\overset{\oplus}{O}H_2$
$-H_2O$
$Me_2\overset{\oplus}{N}{=}CH_2$
(electrophile)
$CH_2{=}\overset{\oplus}{N}Me_2$
CH_2NMe_2
H
$-H^{\oplus}$
CH_2NMe_2

(viii) Acylation

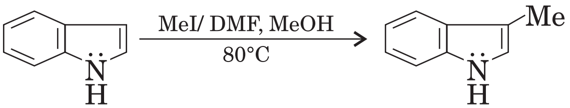


Indole 3-Acetylindole

Mechanism of the reaction

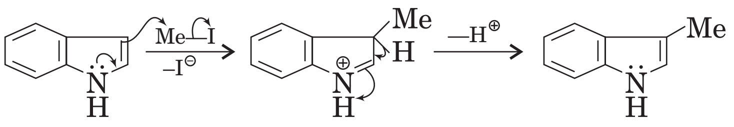

Indole
+ $CH_3{-}C{-}O{-}C{-}CH_3$
O O H—OAc
O
C—CH_3
H
+ $:\ddot{O}Ac^{\ominus}$ + CH_3COOH
O
C—CH_3
+ AcOH

(ix) Alkylation

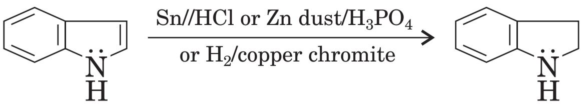


3-Methylindole
or skatole

Mechanism of the reaction



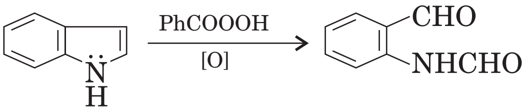
2. Reduction Indole is reduced electronically, by tin and hydrochloric acid, or by zinc and phosphoric acid to 2,3-dihydroindole (*indoline*). This is also produced by the catalytic reduction using copper chromite.



Indole 2,3-Dihydroindole

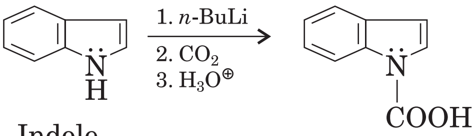
When the reduction is carried out with H_2/Raney nickel, the product is octahydroindole.

3. Oxidation



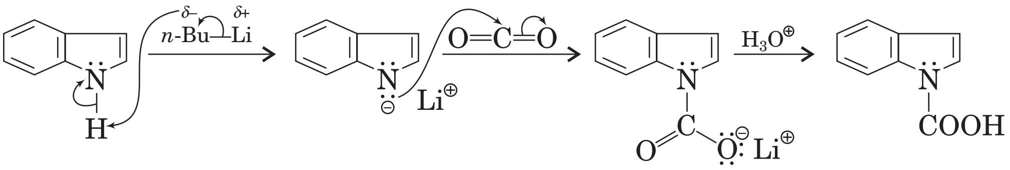
Indole 2-Formamidobenzaldehyde

4. Acidic properties The NH proton of indole is sufficiently acidic to be abstracted by base like *n*-BuLi. This provides a very good method for the synthesis of indole-*N*-carboxylic acids.

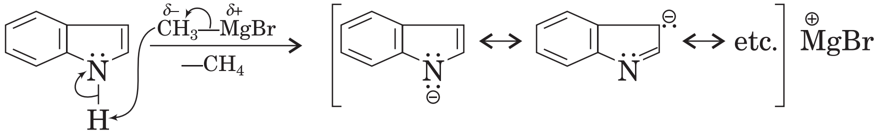


Indole Indole-*N*-carboxylic acid

Mechanism of the reaction

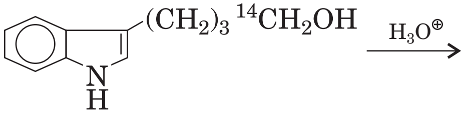


When indole is treated with MeMgBr, indole magnesium bromide is formed. This is used to prepare substituted indoles.

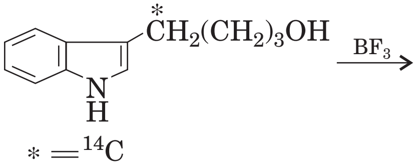


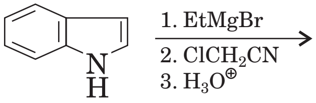
SOLVED PROBLEMS

1. **Predict the product and suggest a reasonable mechanism for each of the following reactions:**

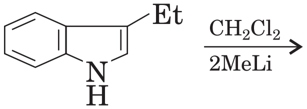
(a)


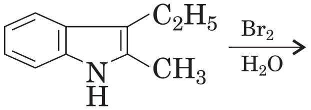
[C.U. 2013]

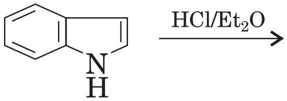
(b)


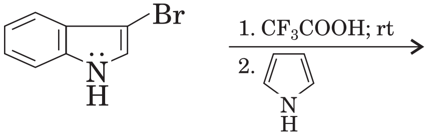
(c)


[C.U. 2014]

(d)


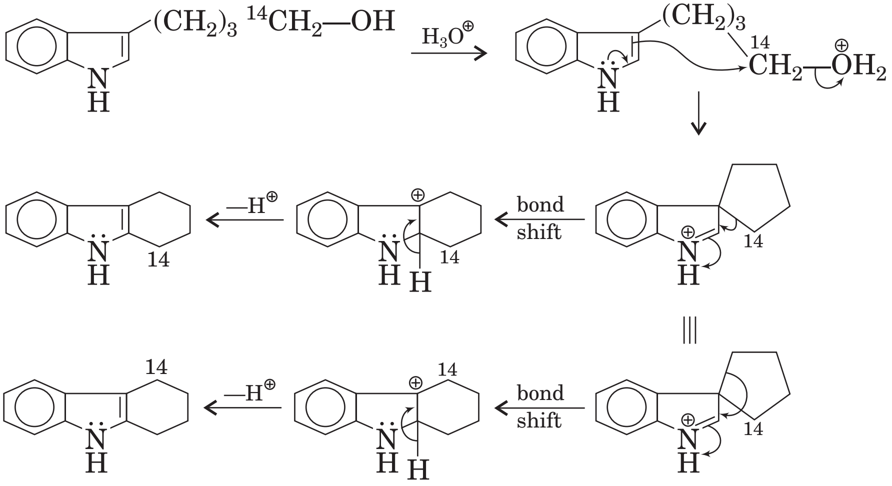
(e)


(f)


(g)


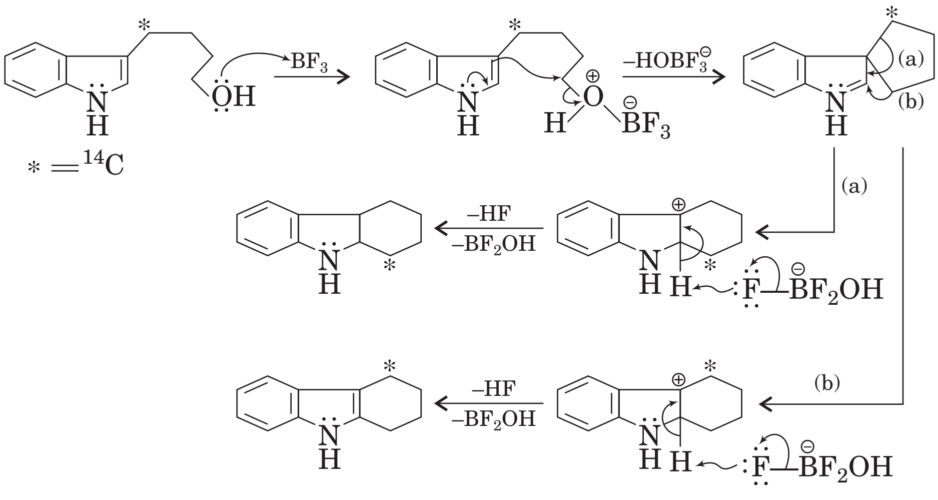
Solution

(a)

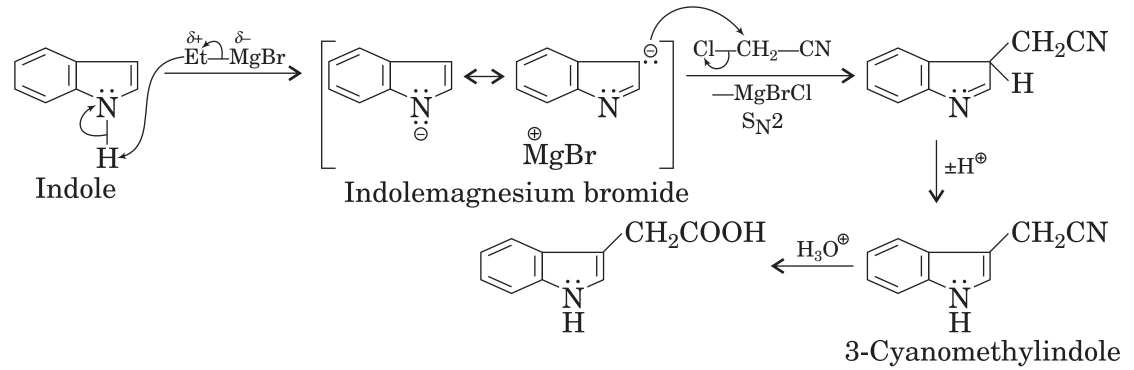


The protonated alcohol undergoes intramolecular nucleophilic substitution to give a spirocyclic intermediate which rearranges (*Plancher rearrangement*) to give the product with differently labelled carbons.

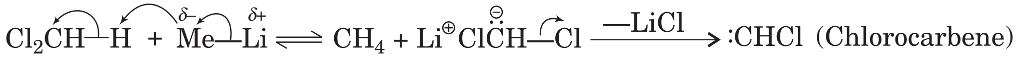
(b) This is similar to problem (a); a Lewis acid is used instead of a proton acid.



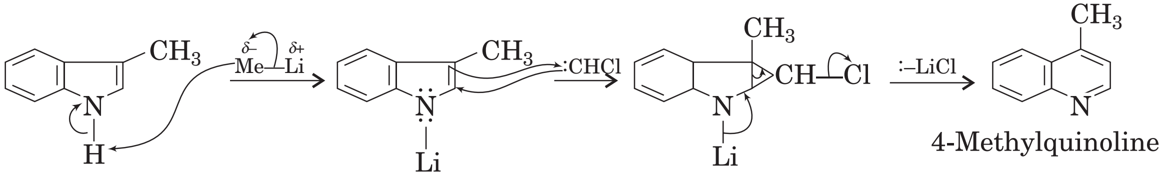
(c) Indole reacts with ethylmagnesium bromide to form another Grignard reagent, which reacts with $ClCH_2CN$ by an S_N2 mechanism to give 3-cyanomethylindole.



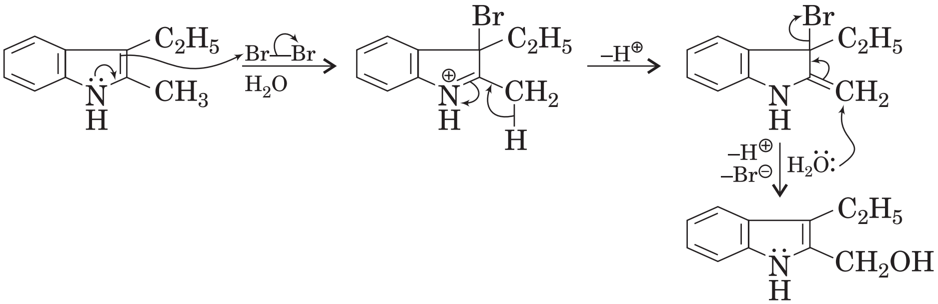
(d) Since the 3-position of the substrate is blocked, only 4-methylquinoline is obtained by an electrophilic addition followed by cleavage of the cyclopropane ring.



$Cl_2CH-H + \overset{\delta-}{Me}-\overset{\delta+}{Li} \rightleftharpoons CH_4 + Li^{\oplus}Cl\overset{\ominus}{C}H-Cl \xrightarrow{-LiCl} :CHCl$ (Chlorocarbene)

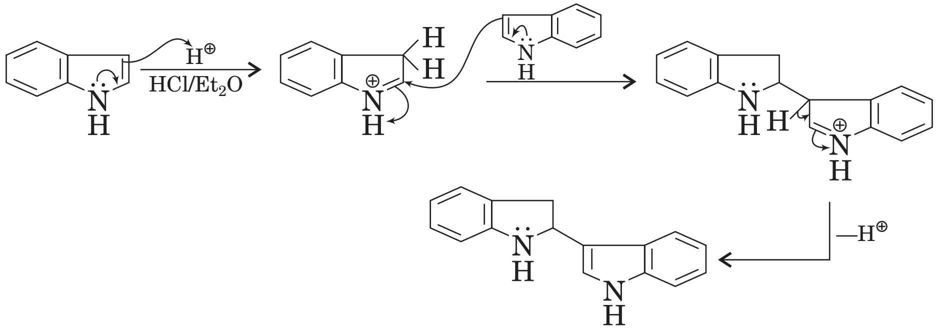


(e)



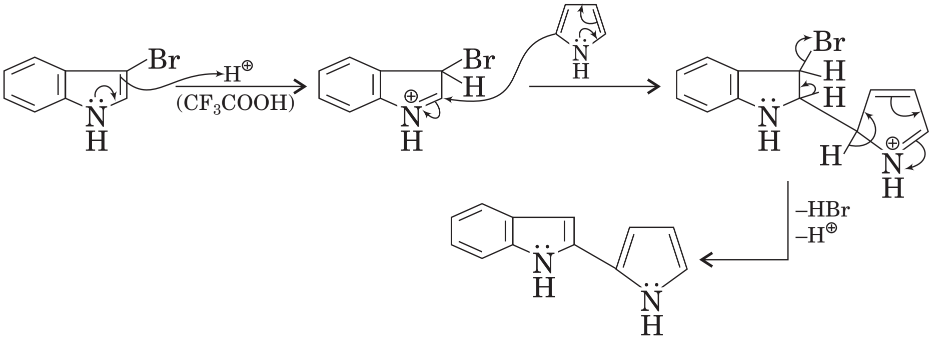
Due to presence of an alkyl group in 3-position, the intermediate loses a proton to form an enamine instead of aromatization. The enamine then undergoes nucleophilic attack by water to form an indole derivative by expulsion of $Br^{\ominus}$.

(f) Indole undergoes acid-catalyzed dimerization in which a protonated indole acts as the electrophile.



Indole dimer
(isolated as its hydrochloride)

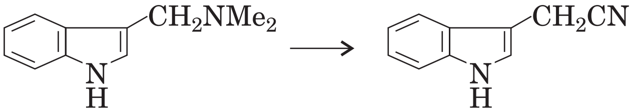
(g)



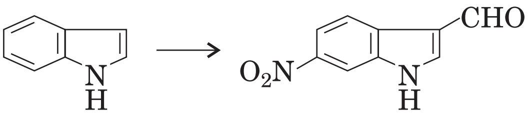
Pyrrole reacts with the protonated 3-bromoindole to give an intermediate which undergoes rearomatization by the loss of a proton and a molecule of HBr to give a 2-substituted indole.

2. How would you carry out the following transformations?

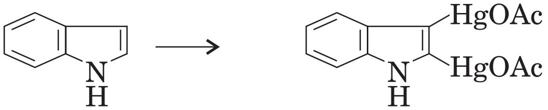
(a)



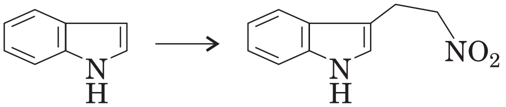
(b)



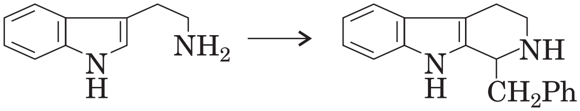
(c)



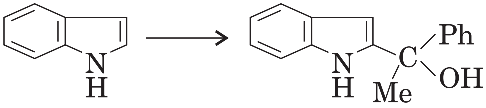
(d)



(e)

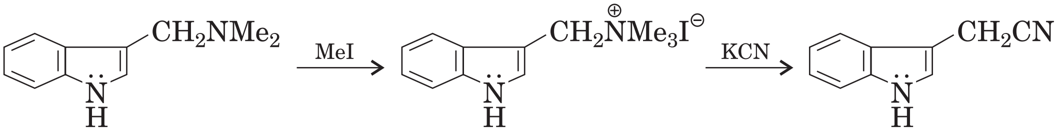


(f)

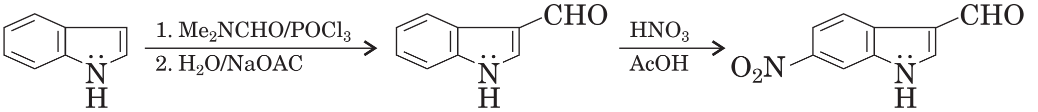


Solution

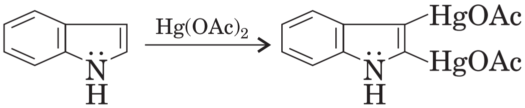
(a)



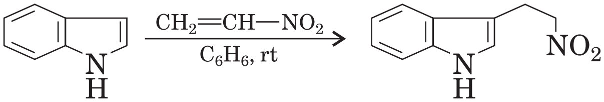
(b)



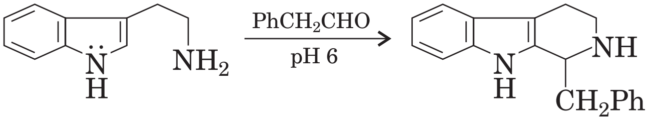
(c)



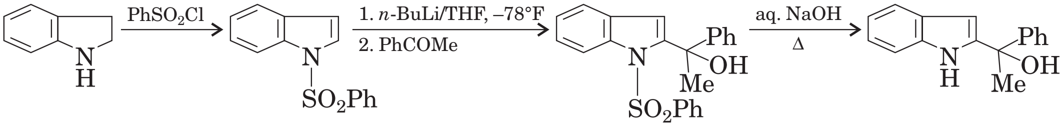
(d)



(e)

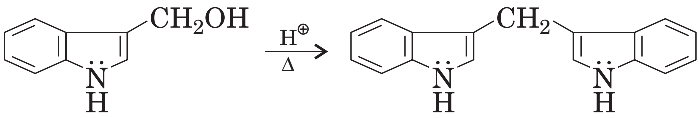


(f)

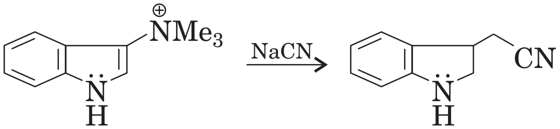


3. Suggest a mechanism for each of the following transformations:

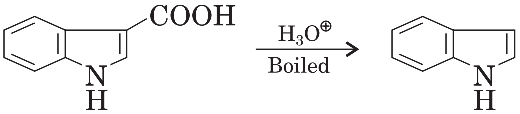
(a)

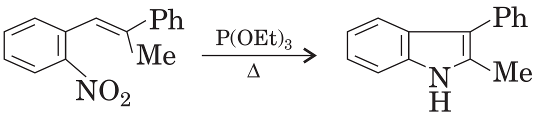


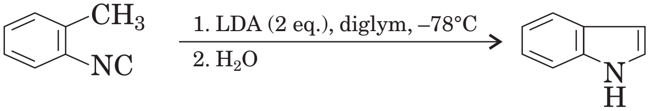
(b)



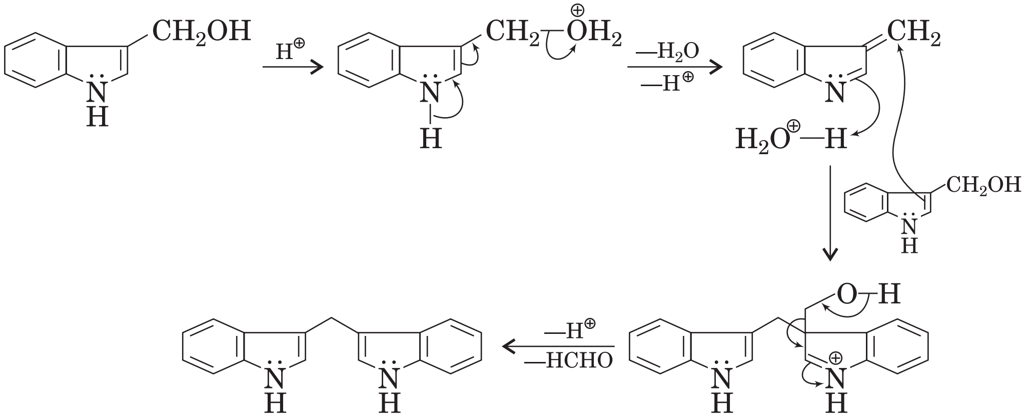
(c)

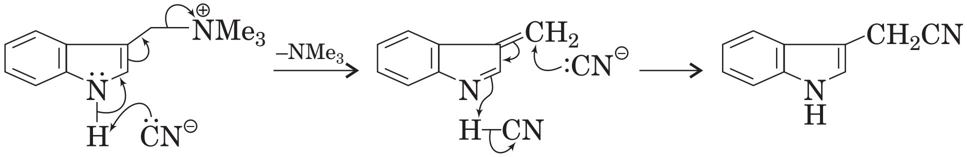


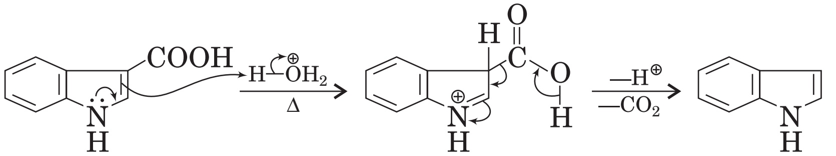
(d) 

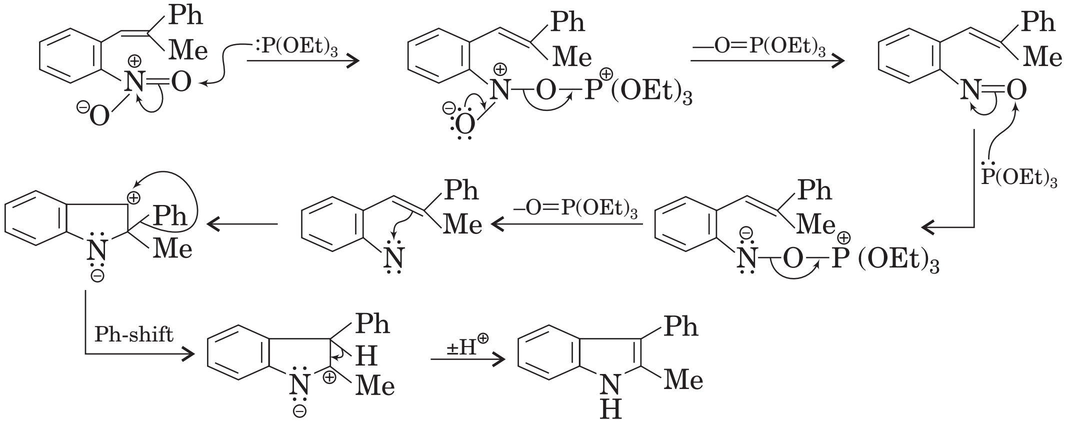
(e) 

Solution

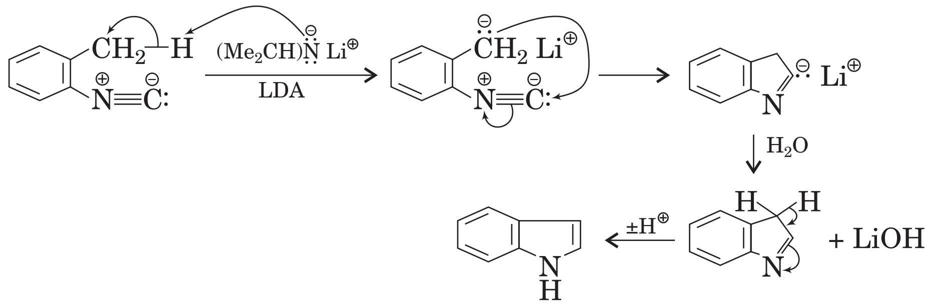
(a) 

(b) 

(c) 

(d) 

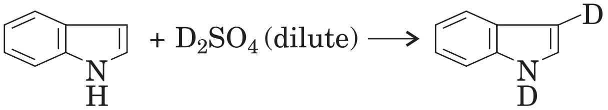
(e)



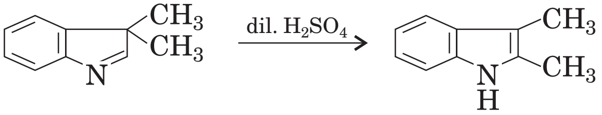
STUDY PROBLEMS

1. At what position is electrophilic substitution of indole fastest? Give your reasoning.
2. Where does indole protonate and why?
3. How can the following compounds be prepared from indole: (i) 3-dimethylaminomethylindole, (ii) 1-methylindole, (iii) 3-acetylindole, (iv) 1-indolecarboxylic acid and (v) 3-indolecarboxylic acid
[**Hint:** (iv) Lithio-indole (obtained by the reaction with *n*-BuLi) reacts with CO_2, predominantly at the N atom and (v) indolemagnesium bromide (obtained by the reaction with CH_3MgBr) reacts mainly at the β-carbon atom.]
4. Predict the structures of the phenylhydrazones required for the Fischer indole synthesis of: (a) 3-ethyl-2-phenylindole; (b) 2-ethyl-3-methylindole; (c) 3-methylindole; (d) 2-phenylindole and (e) indol-3-ylacetic acid.
5. Predict the structure of 'indole trimer' ($C_{24}H_{21}N_3$) which is expected to be formed when indole dimer is subjected to acid treatment.
6. Outline a rational mechanism for each of the following reactions:

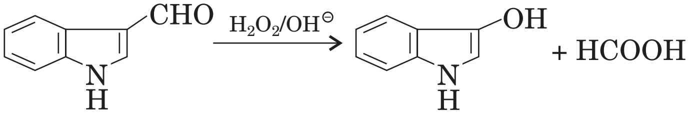
(a)



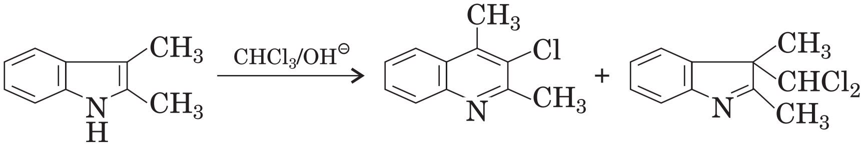
(b)

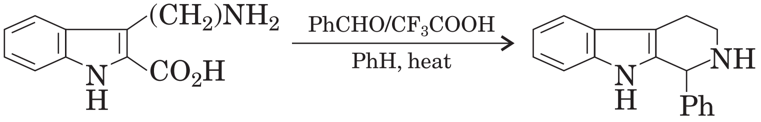


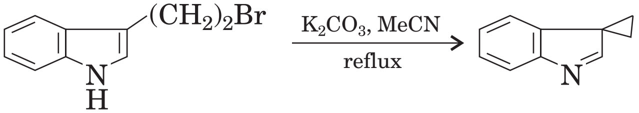
(c)

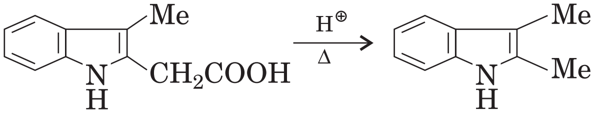


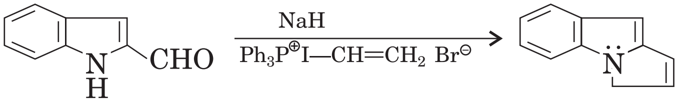
(d)



(e) 

(f) 

(g) 

(h) 

[**Hint:** (h) Intra-molecular Wittig of *N*-substituted indole.]

7. 2-Methylindole is more basic than indole – Why?

8. Electrophilic attack takes place at C-2 in pyrrole, but C-3 in indole. Explain. **[C.U. 2011]**

[**Hint:** See **articles no. 6.2.1.2** and **6.4.1.2**]

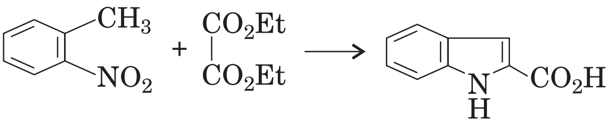
9. 2-Methylindole is more basic than 3-methylindole. Explain. **[C.U. 2011, 2015]**

[**Hint:** The conjugate acid obtained on protonation at C-3 of 2-methylindole is relatively more stable than the conjugate acid obtained on protonation at C-3 of 3-methylindole.]

10. In Fischer indole synthesis, a phenylhydrazone is converted to an indole by the action of an acid. Write the mechanism involved. **[C.U. 2012]**

[**Hint:** See **article no. 6.4.1.1**]

11. Show the complete mechanistic pathway of the following conversion along with the necessary reagents.

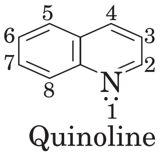


[C.U. 2014]

[**Hint:** See **article no. 6.4.1.1** (Reissert synthesis).]

6.4.2 Quinoline and Its Derivatives

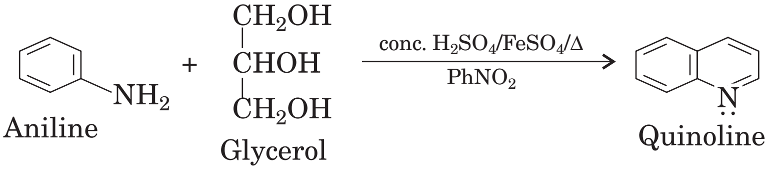
Quinoline is present in coal-tar and bone oil and was first obtained from the alkaloid *quinine* by alkaline decomposition. It is obtained commercially from coal-tar, or prepared synthetically from benzene derivatives by ring closure which can be effected by a number of procedures.



Quinoline

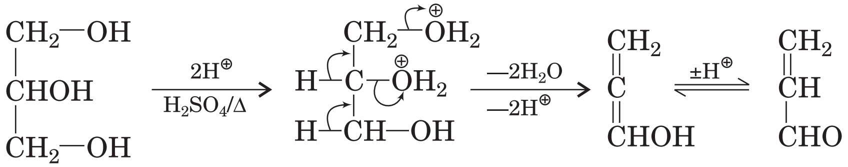
6.4.2.1 Synthetic Methods

1. The Skraup Synthesis This widely used and important synthetic route to quinoline and many of its derivatives involves heating a primary aromatic amine possessing at least one vacant *ortho* position with glycerol, conc. sulphuric acid (a condensing agent) and nitrobenzene (an oxidizing agent). $FeSO_4$ is often used to make the reaction less violent. Quinoline itself may be obtained when a mixture of aniline, nitrobenzene, glycerol, conc. H_2SO_4 and ferrous sulphate is heated in the presence of $PhNO_2$.

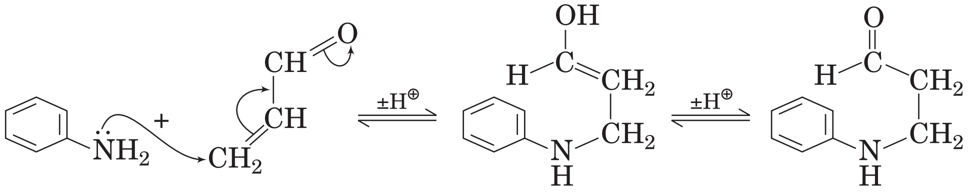


Mechanism of the reaction This synthesis may be envisioned as taking place in four distinct steps:

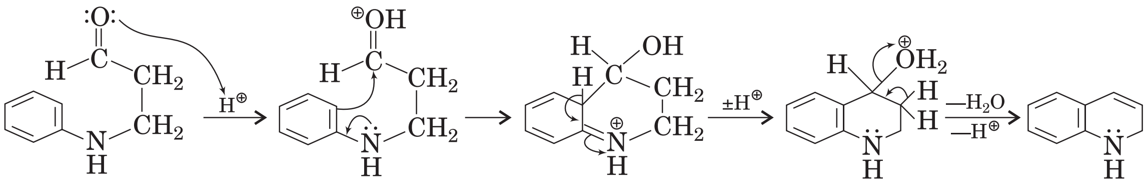
(i) Acid-catalyzed dehydration of glycerol to form acrolein ($CH_2{=}CHCHO$).



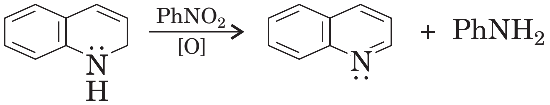
(ii) Michael addition of aniline to acrolein to yield *β*-phenylaminopropionaldehyde.



(iii) Intramolecular electrophilic substitution followed by dehydration to yield 1,2-dihydroquinoline.

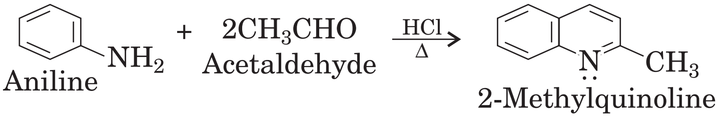


(iv) Oxidation of 1,2-dihydroquinoline by nitrobenzene to give quinoline.

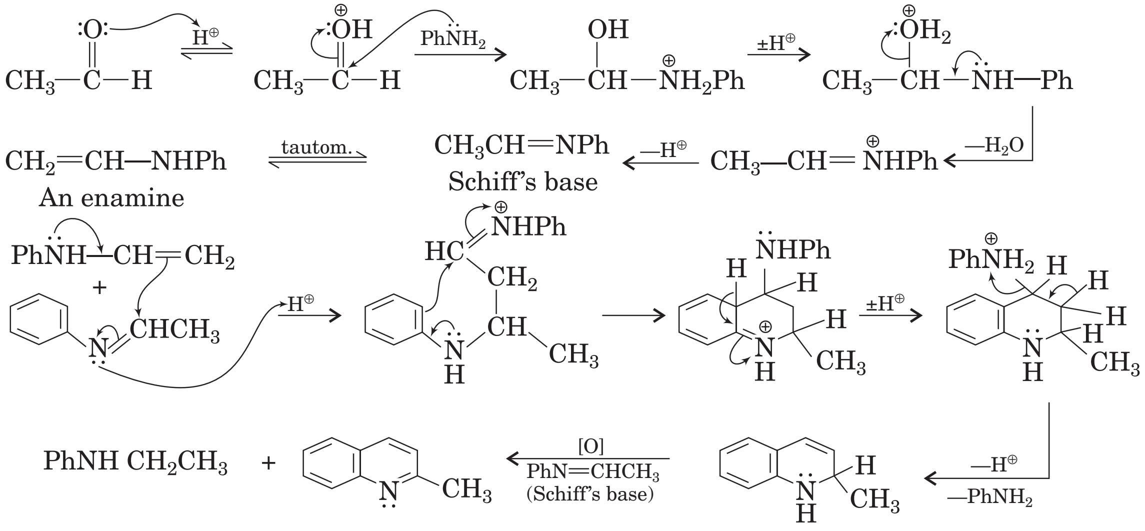


It is to be noted that if a strong *o*-/*p*-directing group is present in the *m*-position, e.g., —OMe, of aniline, then the 7-substituted quinoline is formed; if weakly *o*-/*p*-directing, e.g., Cl, then both 5- and 7-substituted quinolines are formed. If the *m*-substituent is *m*-directing, then 5-substituted quinoline is produced predominantly.

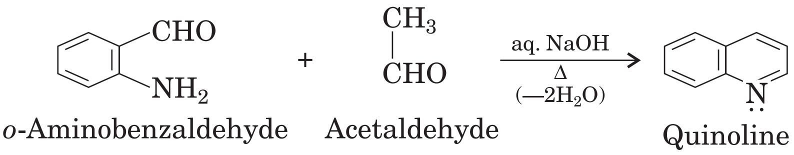
2. The Doebner–Miller Synthesis It is closely related to the Skraup synthesis as an aromatic primary amine is also utilized in this process which proceeds through the intermediate formation of a dihydroquinoline. It consists of heating a primary amine with an aldehyde (2 moles) in the presence of hydrochloric acid. The oxidizing agent involved is a Schiff's base. For example:



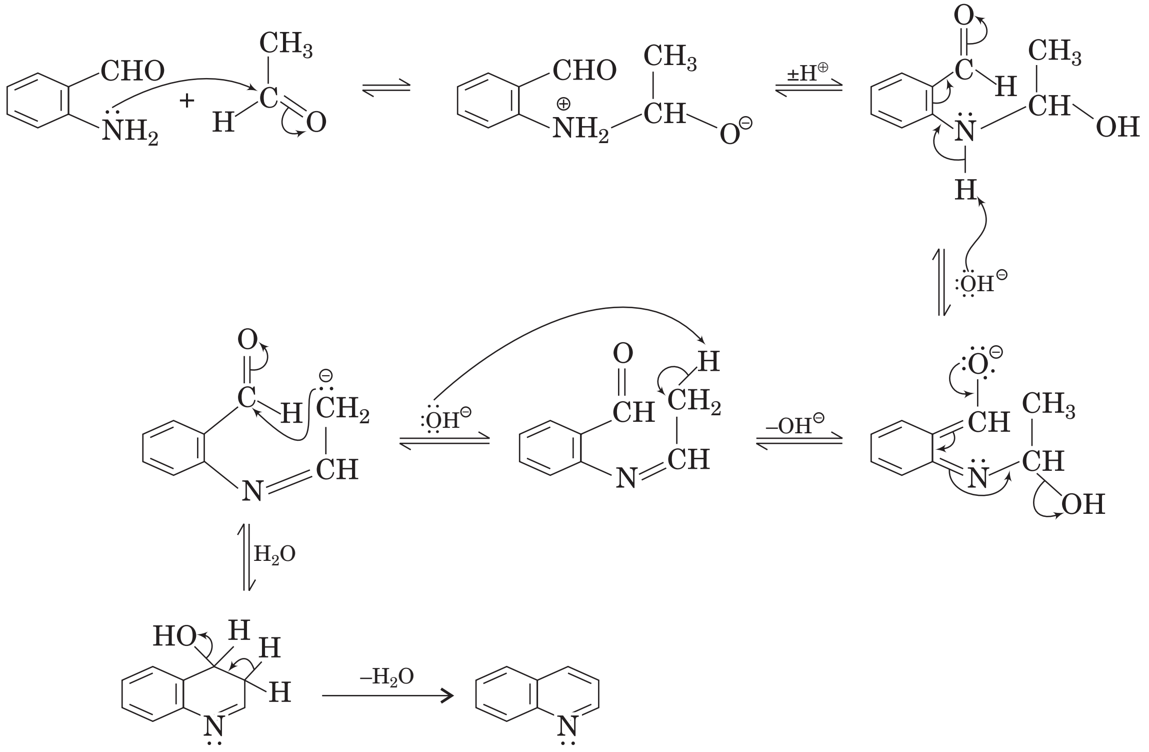
Mechanism of the reaction From recent investigations it becomes clear that the process involves self condensation of two molecules of Schiff's base (one in the form of enamine) to form the quinoline nucleus. The Schiff's base also functions as the oxidizing agent and converts the dihydroquinoline to quinoline.



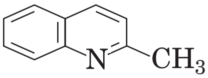
3. The Friedländer Synthesis This is another important method for synthesizing quinoline and many of its derivatives. This involves a condensation reaction between an aliphatic carbonyl compound containing an α-H atom and an aromatic carbonyl compound with an —NH_2 group at the *ortho* position in the presence of a base. For example, quinoline is formed when *o*-aminobenzaldehyde is condensed with acetaldehyde in aqueous sodium hydroxide.



Mechanism of the reaction The reaction involves formation of a Schiff's base followed by an internal aldol type condensation between the aryl carbonyl group and the methyl group with considerably acidic hydrogens.



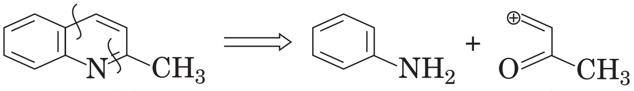
Synthesis of Some Quinoline Derivatives (Target Molecules) through Disconnection Approach

1.  (2-Methylquinoline)

TM (1)

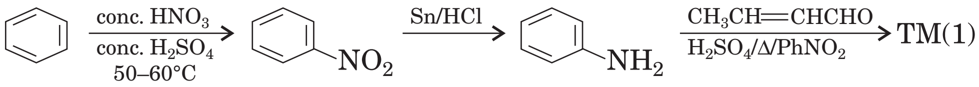
Retrosynthetic analysis

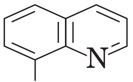
This target molecule might be disconnected to give aniline and a synthon A.



The simplest answer for A is to use crotonaldehyde, $CH_3CH{=}CHCHO$, and oxidize. This is the basis of what is called the Skraup synthesis of quinoline.

Synthesis

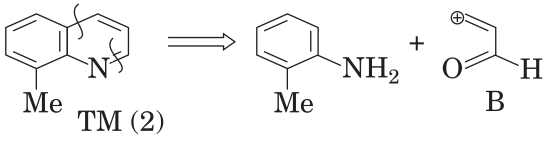


2.  (8-Methylquinoline)

Me TM(2)

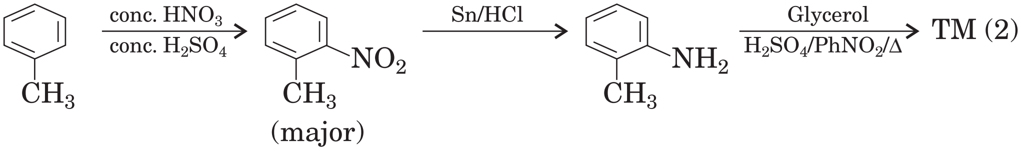
Retrosynthetic analysis

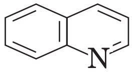
The target molecule might be disconnected to give *o*-toluidine and a synthon B.



The simplest answer for B is to use acrolein, $CH_2{=}CHCHO$, and oxidize. This is also a Skraup synthesis of quinoline.

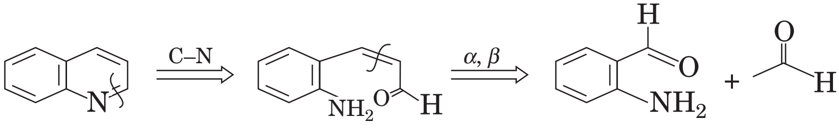
Synthesis



3.  (Quinoline)

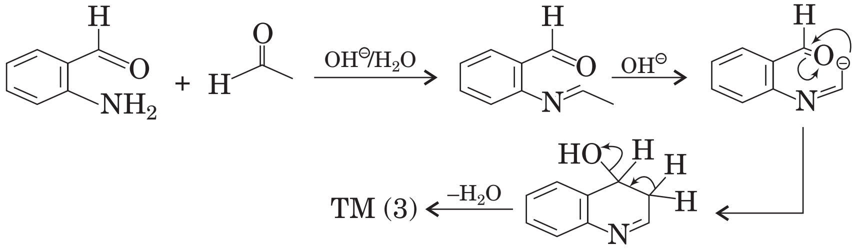
TM (3)

Retrosynthetic analysis



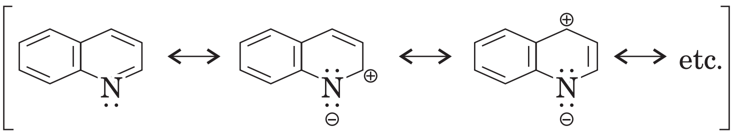
When *o*-aminobenzaldehyde is condensed with acetaldehyde in the presence of dilute alkali, quinoline is obtained. This is the basis of what is called the Friendlander’s synthesis of quinoline.

Synthesis



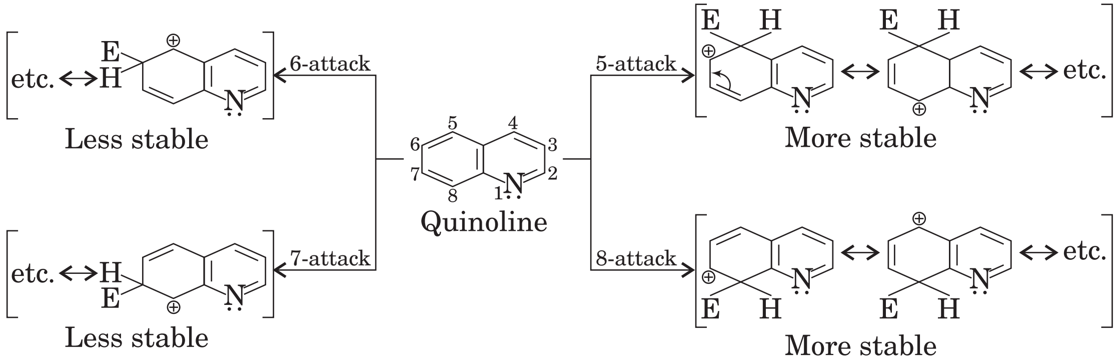
6.4.2.2 *Properties and Reactions*

Quinoline is a colourless liquid having b.p. 237°C and has a characteristic smell resembling that of pyridine. It is weakly basic ($\mathrm{p}K_\mathrm{a}$ 4.94). Presence of electron-donating groups at the 2- and 4-position increases its basicity. Quinoline is highly aromatic and has a resonance energy of 47.3 kcal/mol and is considered a resonance hybrid of the following principal resonance structures.



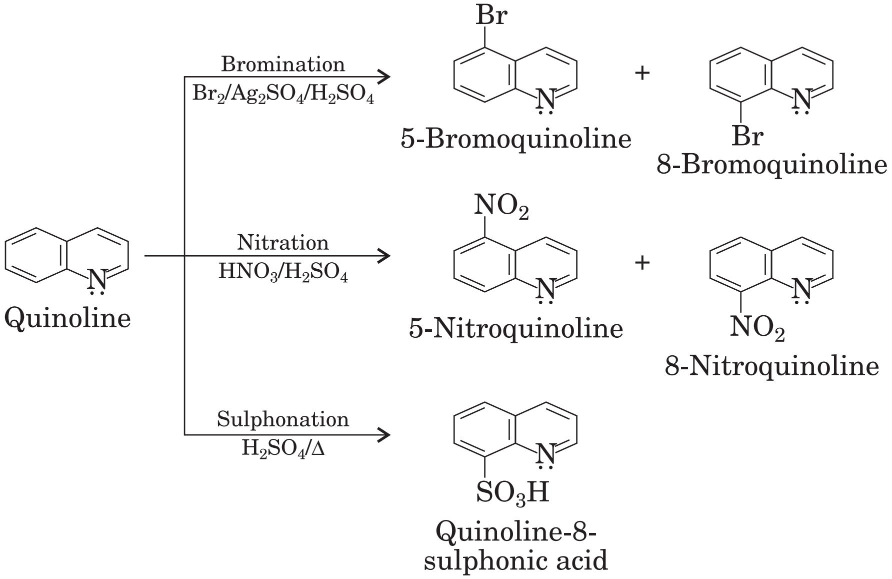
The dipole moment (μ) of quinoline is 2.10D, which indicates charge separation in the ring.

1. Electrophilic substitution The nitrogen containing ring of quinoline resembles pyridine and is π-electron-deficient and more so by protonation of the ring nitrogen atom. Thus, acidic electrophilic reagents show a strong preference for attack in the carbocyclic ring resembling benzene and nucleophilic reagents show a strong preference for attack in the nitrogen containing ring. The electrophilic substitution occurs preferably at C-5 and C-8 positions. This may be explained in term of the stability of the carbocation intermediates obtained on electrophilic attack.



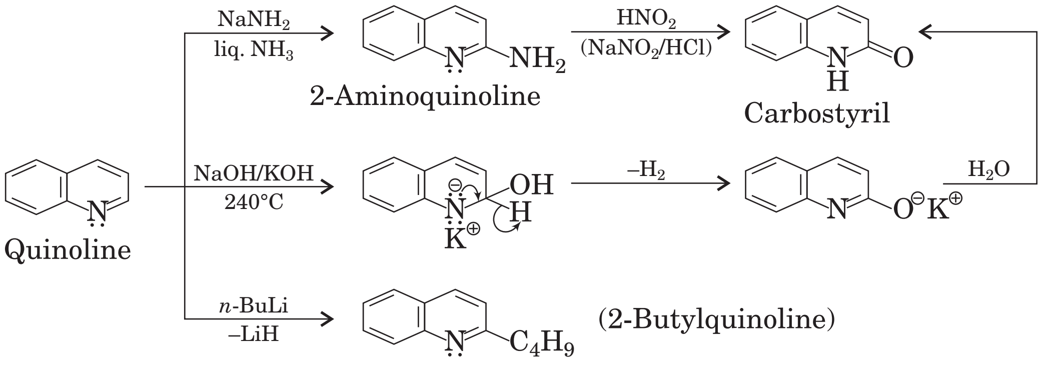
The carbocation intermediate for 5- or 8-attack contains two resonance structures in which the aromaticity of the nitrogen containing ring is still preserved, whereas the intermediates for 6- and 7-attack contain only one resonance structure in which the aromaticity of the nitrogen containing ring is preserved. Therefore, the intermediates for 5- and 8-attack are relatively more stable and so, the electrophilic substitution occurs mainly at 5- and 8-positions.

Quinoline undergoes electrophilic substitutions like halogenation, nitration and sulphonation. It requires less vigorous conditions for electrophilic substitution than those required for pyridine.



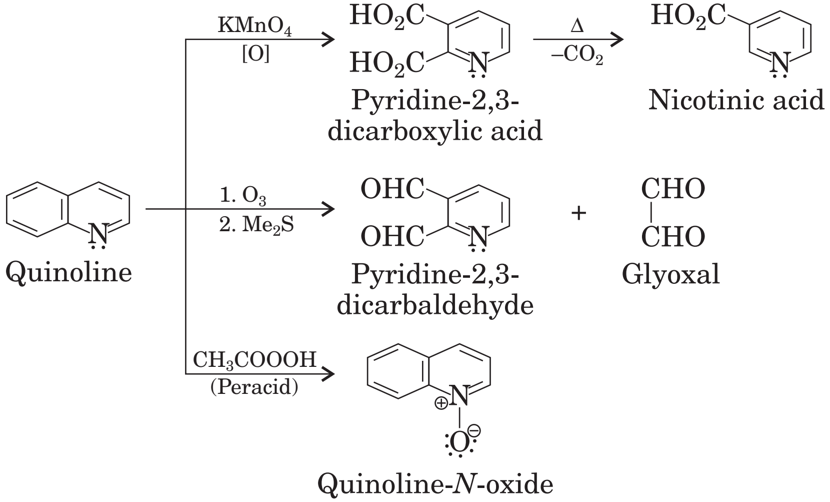
Sulphonation of quinoline with H_2SO_4 at 300°C gives quinoline-6-sulphonic acid, which can also be obtained when quinoline-8-sulphonic acid is heated at 300°C. When quinoline-8-sulphonic acid is heated with solid NaOH and then acidified, 8-hydroxyquinoline is obtained.

2. Nucleophilic substitution Like pyridine, quinoline also undergoes nucleophilic substitution reactions. Sodium amide, a strong nucleophilic reagent, causes substitution at 2-position yielding 2-aminoquinoline which on further treatment with nitrous acid ($NaNO_2$ plus HCl) gives an important compound known as *carbostyril*. Similarly, 2-butylquinoline can be obtained when quinoline is treated with *n*-butyllithium.



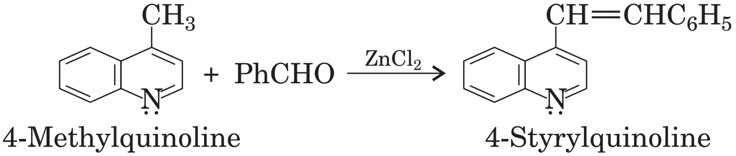
The mechanisms of these reactions are shown in the case of pyridine (**article no. 6.3.1.2**).

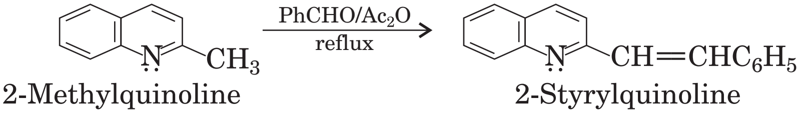
3. Oxidation Different products are obtained when quinoline is oxidized using different oxidizing agents and reaction conditions.



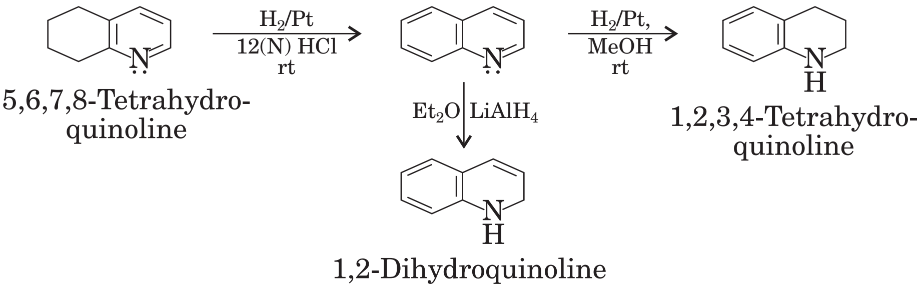
As the benzenoid ring is more electron rich, it is more easily attacked by the oxidizing agents to give the corresponding products. However, peracids oxidize the pyridine ring by forming an *N*-oxide.

4. Side chain reactivity The alkyl groups present at the *ortho*- or *para*- to the ring nitrogen in quinoline are considerably acidic and therefore, the chemical reactivity of such compounds resembles rather closely that of 2- and 4-alkyl pyridines. For example:





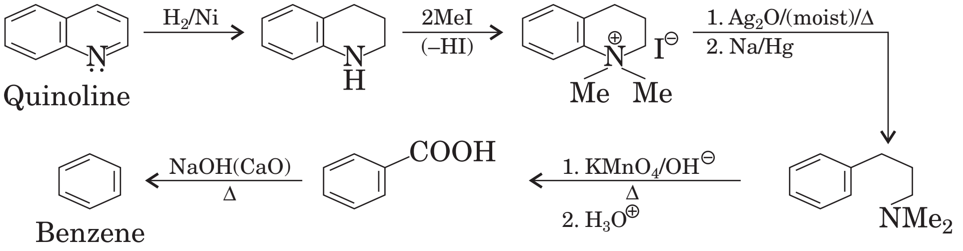
5. Reduction:



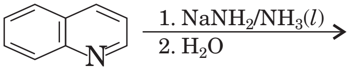
SOLVED PROBLEMS

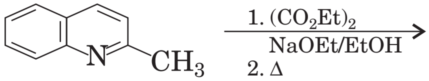
1. **How would you prove that quinoline bears a benzene nucleus in its molecule?**

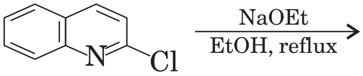
Solution When quinoline is treated sequentially with H_2/Ni, MeI, moist Ag_2O/Δ, Na/Hg and $KMnO_4$, benzoic acid is obtained. This on heating with sodalime produced benzene. This observation, therefore, suggests that benzene nucleus is a part of quinoline molecule.

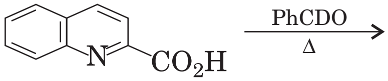


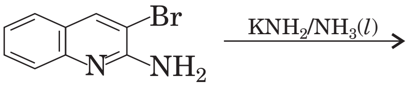
2. **Predict the product and suggest a reasonable mechanism for each of the following reactions:**

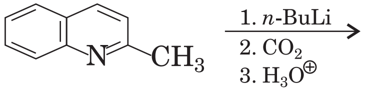
(a)


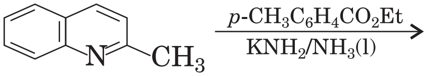
(b)


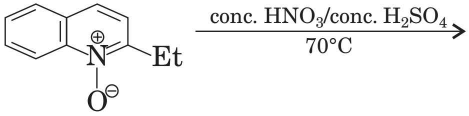
(c)


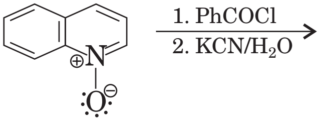
(d)


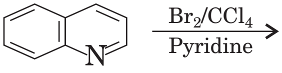
(e)


(f)


(g)


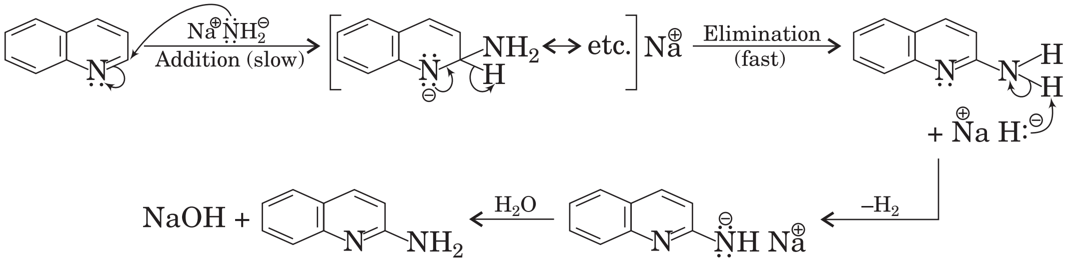
(h)


(i)


(j)


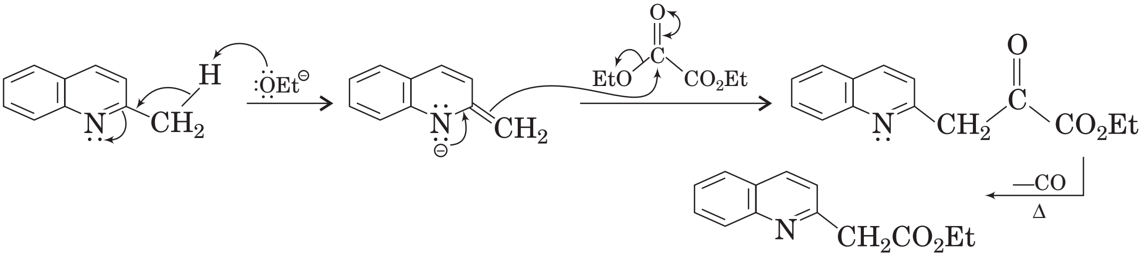
Solution

(a) Quinoline undergoes nucleophilic attack at 2-position to yield 2-aminoquinoline.

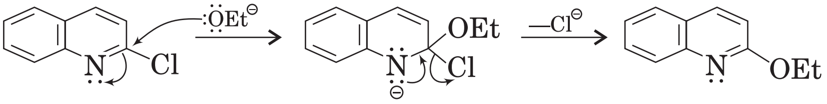


$Na^{\oplus}NH_2^{\ominus}$
Addition (slow)
NH_2
H
etc.
$Na^{\oplus}$
Elimination
(fast)
N
H
H
+ $Na^{\oplus}$ $H^{\ominus}$
$-H_2$
$NH^{\ominus}$ $Na^{\oplus}$
H_2O
NaOH +
NH_2

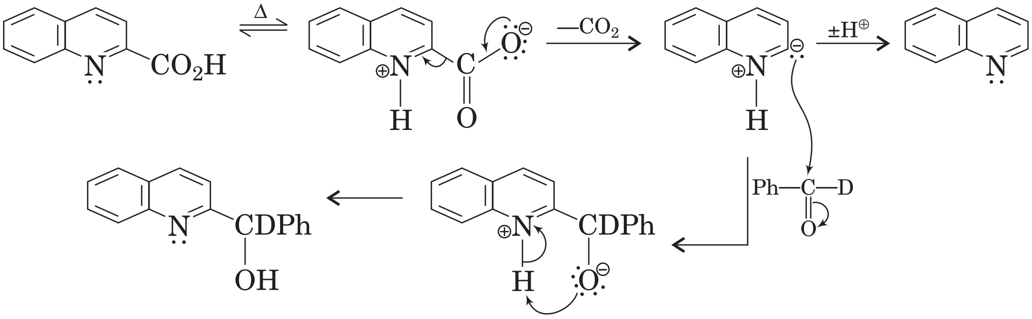
(b) Since the protons of the quinoline-2-alkyl group are particularly acidic, a condensation reaction occurs in the presence of base to give a ketoester which when heated produces the corresponding ester.



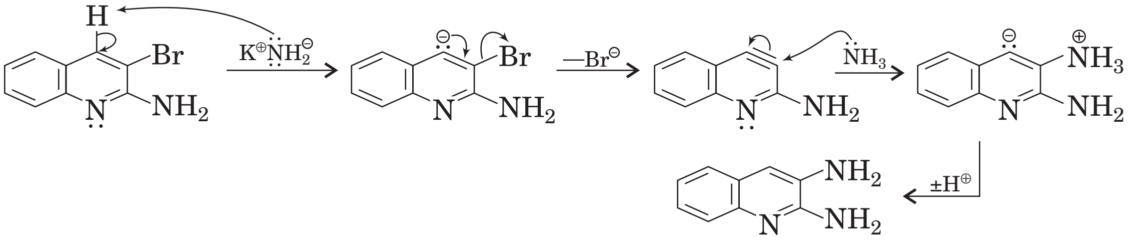
(c) Nucleophilic substitution occurs by the alkoxide ion to give the corresponding ether.



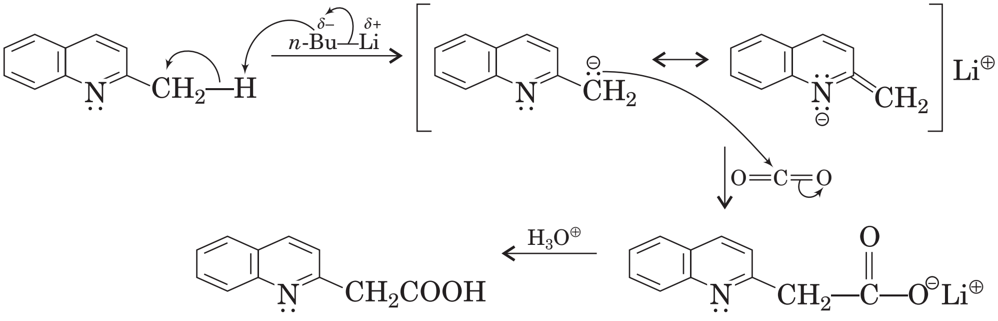
(d) Decarboxylation followed by nucleophilic attack on the carbonyl carbon produces a secondary alcohol. The intermediate zwitter ion may also produce quinoline by proton transfer.



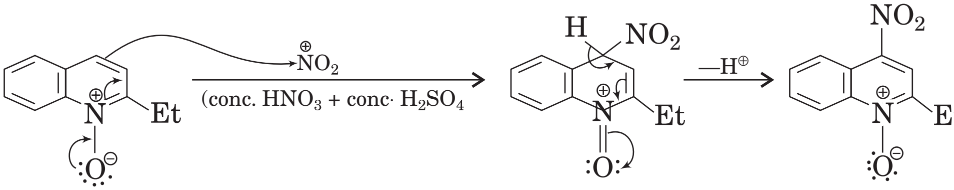
(e) The reaction proceeds through the formation of an aryne intermediate to yield 1,2-diaminoquinoline.



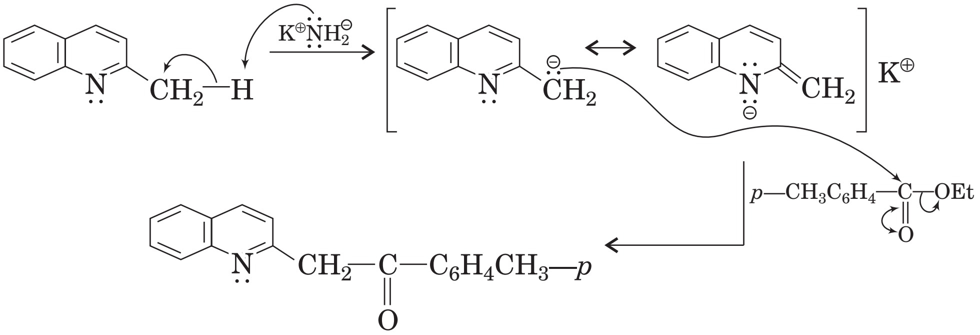
(f) Base abstracts an acidic methyl hydrogen to form a carbanion, which then reacts with CO_2 followed by acidification to give a carboxylic acid.



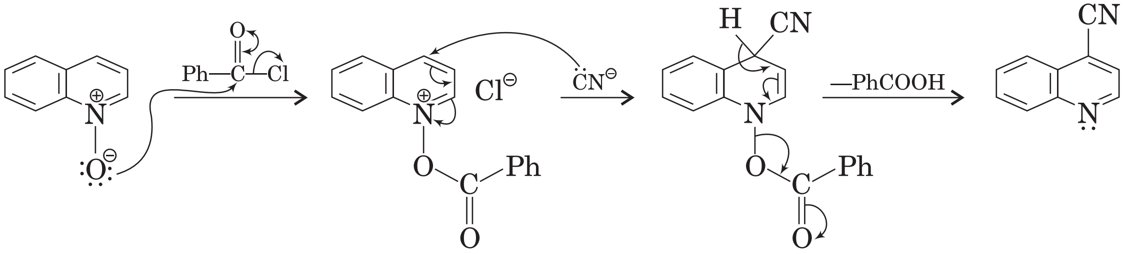
(g) The more activated heterocyclic ring undergoes nitration to give the corresponding nitro derivative.



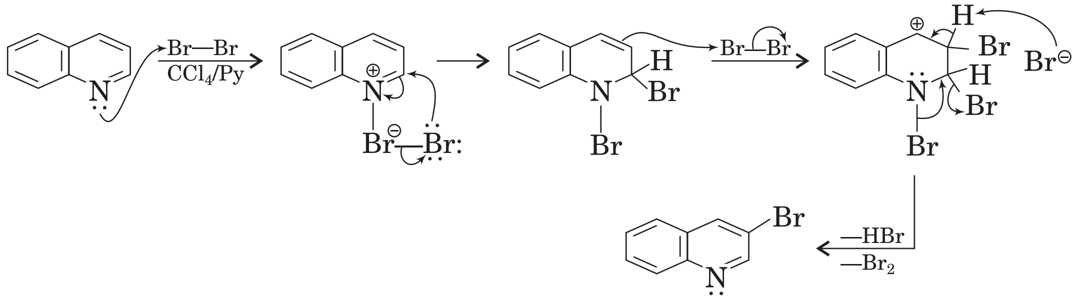
(h)



(i) Benzoylation of the *N*-oxide followed by nucleophilic attack by $CN^{\ominus}$ on C-4 and subsequent loss of benzoic acid produces 4-cyanoquinoline.

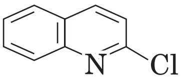


(j) Bromination of quinoline by Br_2/CCl_4 in the presence of pyridine yields 3-bromoquinoline by the following addition–elimination mechanism.

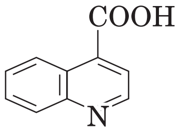


3. How would you convert quinoline to each of the following compounds:

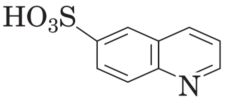
(a)



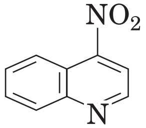
(b)



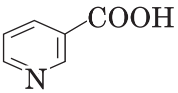
(c)



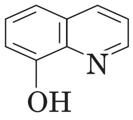
(d)



(e)

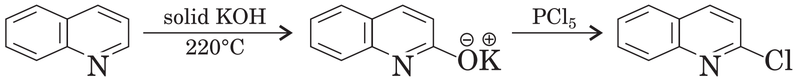


(f)

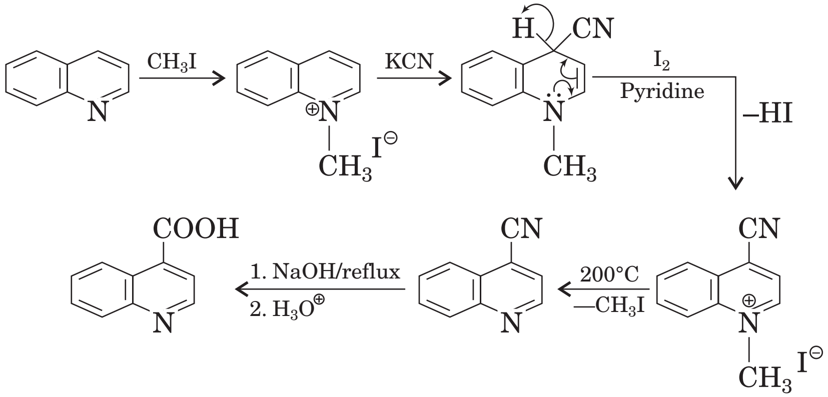


Solution

(a)



(b)



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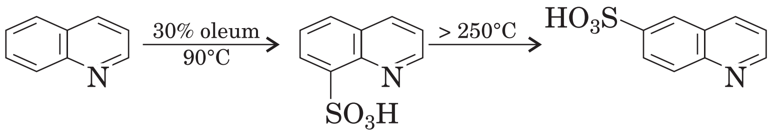

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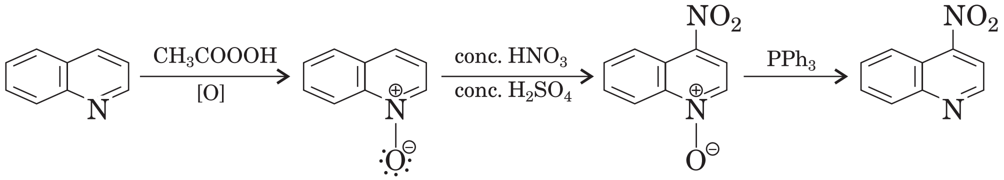

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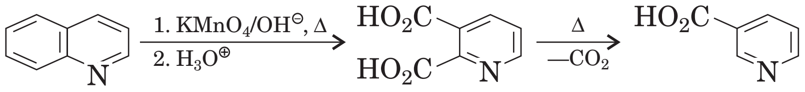

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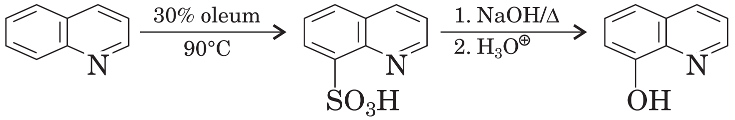


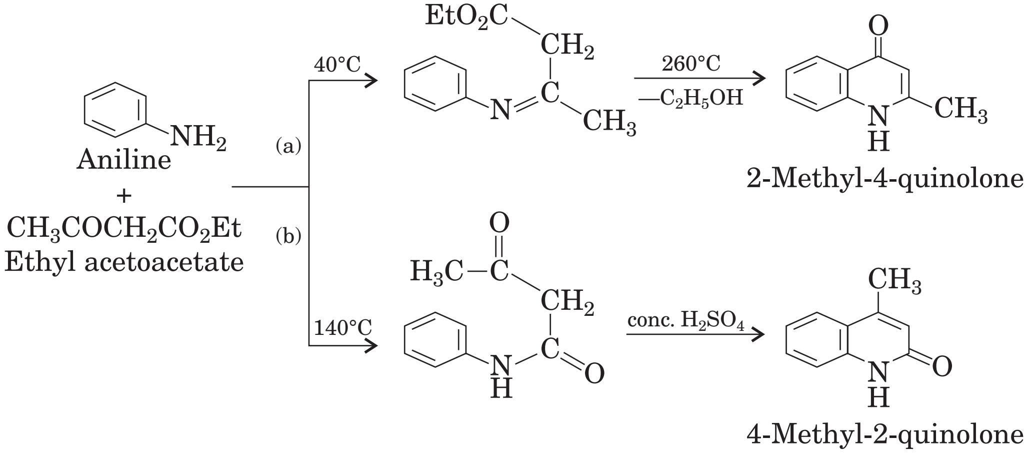
4. **(a) How would you prepare 2-methyl-4-quinolone and 4-methyl-2-quinolone using aniline and ethyl acetoacetate? Give mechanisms of the reactions involved.**

   (b) Convert: aniline → 4-methylquinoline **[C.U. 2010]**

Solution

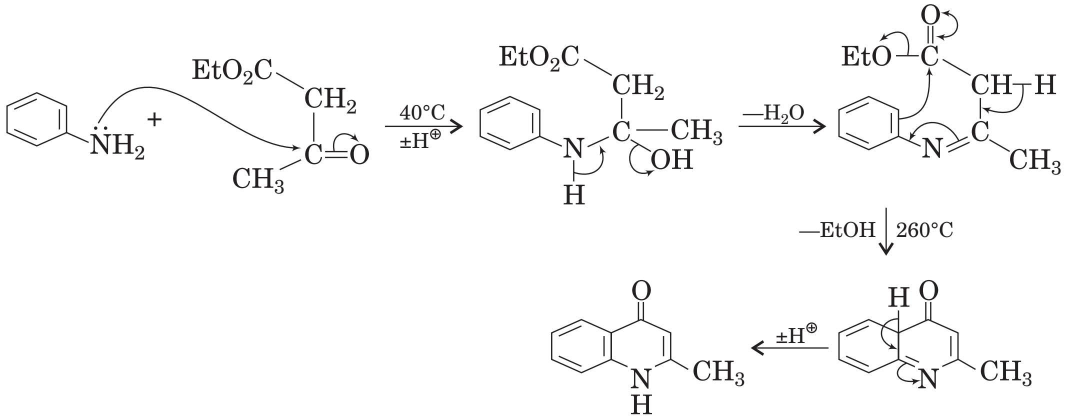
(a) These two quinoline derivatives can be prepared as follows:

(a)



Mechanisms of the reactions

(a)



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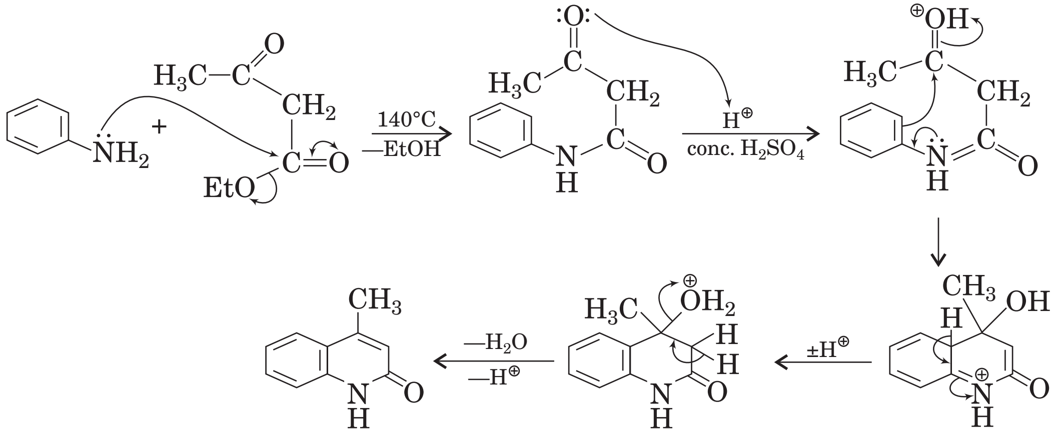
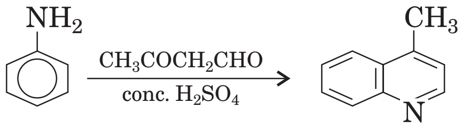


(c)



5. Write structures of the aromatic primary amines required for the Skraup synthesis of the following compounds:

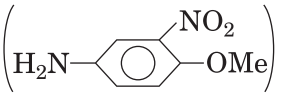
(a) 6-Ethylquinoline **(b) 8-Hydroxyquinoline** **[C.U. 2013]**
(c) 6-Methoxy-8-nitroquinoline **(d) 8-Methylquinoline**
(e) 1-Azaphenanthrene

Solution

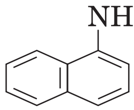
(a) 4-Ethylaniline (p-Et$C_6H_4NH_2$)

(b) o-Aminophenol (o-HO$C_6H_4NH_2$)

(c) 4-Methoxy-2-nitroaniline

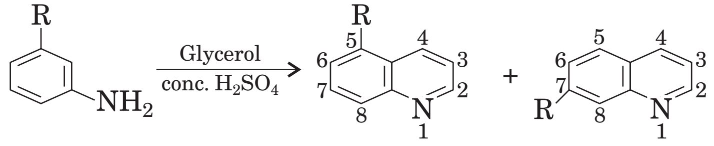


(d) o-Toluidine (o-$CH_3C_6H_4NH_2$)

(e) 1-Naphthylamine 

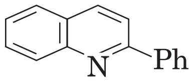
6. Predict the problem which might arise in the application of the Skraup synthesis for the preparation of 5-methylquinoline.

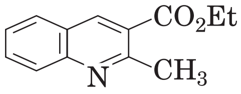
Solution A *meta*-substituted aniline gives rise to a mixture of 5- and 7-substituted quinolines because the ring closure may take place at 2- or 6- positions of aniline.

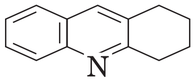


The synthesis of 5-methylquinoline requires *m*-toluidine. Therefore, the synthesis of this quinoline derivative leads to the formation of a mixture of 5- and 7-methylquinoline. As a result, the yield of the desired product is low and its separation from the other product becomes difficult.

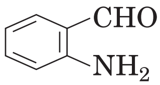
7. Give the starting materials for the synthesis of the following quinoline derivatives by the Friedlander's method:

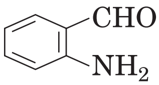
(a) 

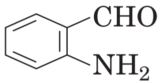
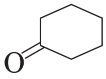
(b) 

(c) 

Solution

(a)  + PhCOCH$_3$

(b)  + CH$_3$COCH$_2$CO$_2$Et

(c)  + 

8. Explain the following observations:

(a) Quinoline is more reactive than pyridine towards electrophilic substitutions.

(b) 8-Aminoquinoline is more basic than 7-aminoquinoline.

(c) 2-Amino-1-methylnaphthalene fails to undergo the Skraup synthesis to give a quinoline derivative. But the same synthesis on 2-amino-3-methylnaphthalene gives the quinoline derivative.

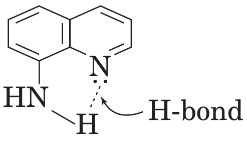
(d) When quinoline is oxidized with permanganate, quinolinic acid is obtained.

(e) Quinoline-2,3-dicarboxylic acid smoothly forms only quinoline-3-carboxylic acid via a selective decarboxylation. [C.U. 2012]

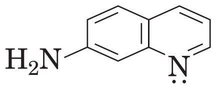
Solution

(a) Because of the presence of electron rich benzene nucleus, quinoline is more reactive than pyridine towards electrophilic substitution.

(b) Because of intramolecular hydrogen bonding, 8-amino-quinoline is a much weaker base than 7-aminoquinoline in which intramolecular H-bonding is not possible.

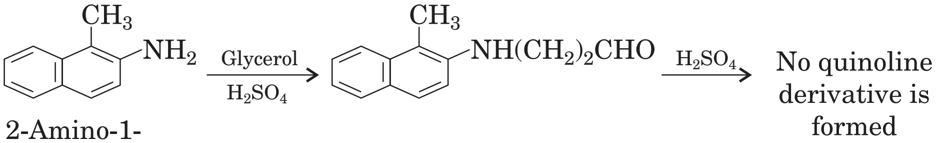


8-Aminoquinoline
($pKa = 3.93$)

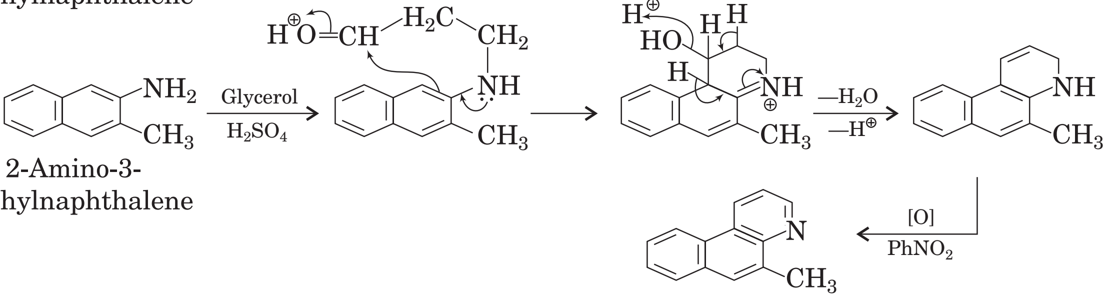


7-Aminoquinoline
($pKa = 6.5$)

(c) Naphthalene in all its reactions behaves as a fixed bond structure where both the rings are benzenoid. α-Substituted naphthalenes do not undergo ring closure because elctrophilic attack at C-3 does not take place. However, in 2-amino-3-methylnaphthalene, the C-1 position is free and ring closure is possible as in the case of normal Skraup synthesis.



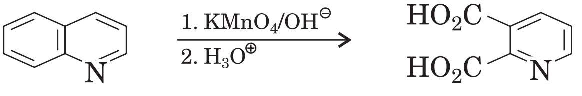
2-Amino-1-methylnaphthalene



2-Amino-3-methylnaphthalene

5-Methylbenzo[f]quinoline

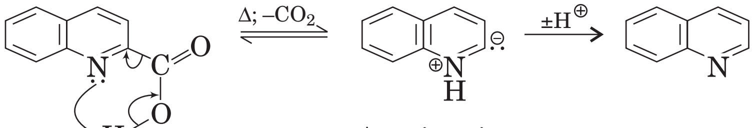
(d) Since the benzene ring of quinoline is relatively electron-rich compared to the pyridine (π-electron-deficient), it undergoes oxidation by permanganate to yield quinolinic acid.



Quinoline

Pyridine-2,3-dicarboxylic acid
(Quinolinic acid)

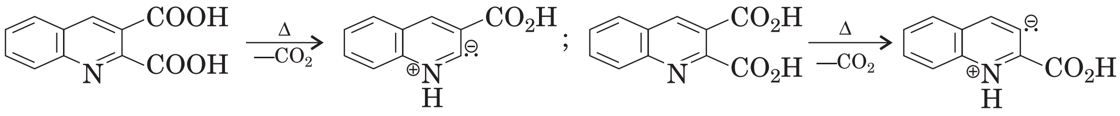
(e) A quinoline carboxylic acid decarboxylates through the formation of a zwitterion in which the negative charge on carbon is stabilized by the –I effect of the positive N-atom. For example:



A zwitterion

Quinoline-2-carboxylic acid

Since the –I effect becomes weaker with distance, the carbanion obtained on decarboxylation of C-2–COOH group is more stable than that obtained on decarboxylation of C-3–COOH group.

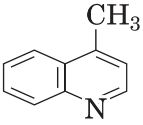


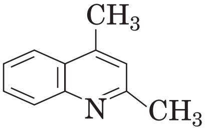
(more stable) (less stable)

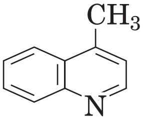
For this reason, quinoline-2,3-dicarboxylic acid smoothly forms only quinoline-3-carboxylic acid via a selective decarboxylation.

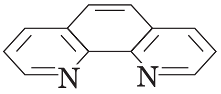
STUDY PROBLEMS

1. How would you synthesize the following quinoline derivatives by the Skraup method?

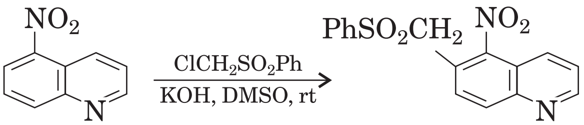
(a) 

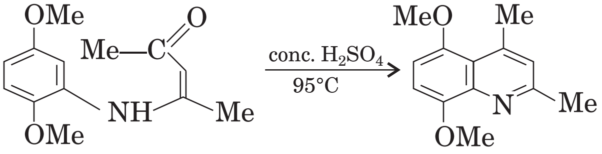
(b) 

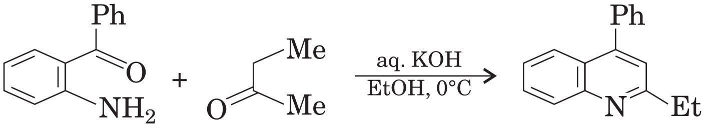
(c) 

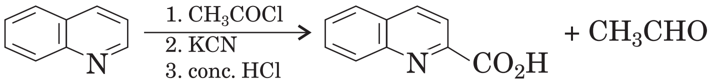
(d) 

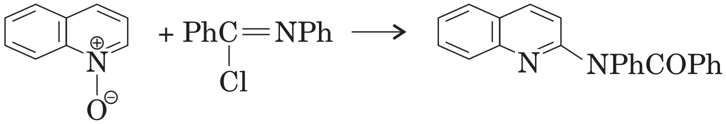
2. Suggest a mechanism for each of the following reactions:

(a) 

(b) 

(c) 

(d) 

(e) 

3. Offer suitable explanation for each of the following observations:
   (a) Acrolein itself is not used in the Skraup synthesis of quinoline.
   (b) Quinoline is more easily reduced than naphthalene.
   (c) Electrophilic attack in quinoline occurs at C-5 and not at C-6 under acidic conditions.
   (d) Nitration of the ring containing the heteroatom in quinoline can be carried out by converting quinoline into quinoline *N*-oxide.

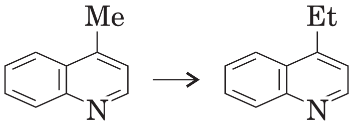
4. Illustrate with examples how quinoline compares with α-nitronaphthalene in electrophilic substitution.

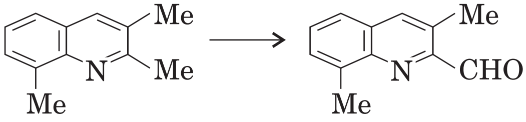
5. Explain why the relative rates of reaction of iodomethane separately with isoquinoline, quinoline, and 8-methylquinoline are 69, 8 and 0.008, respectively.
[**Hint:** There is no question of *peri*-steric hindrance in the case of isoquinoline; there is small *peri*-steric hindrance in the case of quinoline and there is large *peri*-steric hindrance in the case of 8-methylquinoline.]

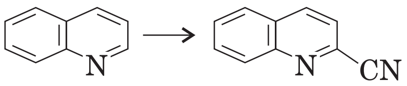
6. Suggest a plausible mechanism to rationalize the formation of methyl 2-methylquinoline-3-carboxylate from the reaction of aniline with methyl acetoacetate and then this with a mixture of DMF and $POCl_3$.

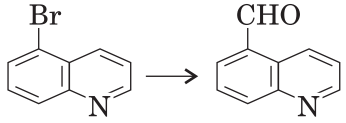
7. How might one selectively reduce the heterocyclic ring of quinoline?

8. How could one convert:

(a) 

(b) 

(c) 

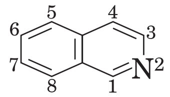
(d) 

9. When aniline and methyl vinyl ketone are used in the Skraup synthesis, the product is 4-methylquinoline and no 2-methylquinoline is obtained. However, when aniline and crotonaldehyde are used, the product is exclusively 2-methylquinoline. What conclusion can be drawn from these observations regarding the mechanism of the Skraup synthesis.

10. Show the complete sequence of the reaction when aniline, conc. H_2SO_4, glycerol, and a mild oxidizing agent are heated together. **[C.U. 2015]**
[**Hint:** See **article no. 6.4.2.1** (Skraup synthesis).]

6.4.3 Isoquinoline and Its Derivatives

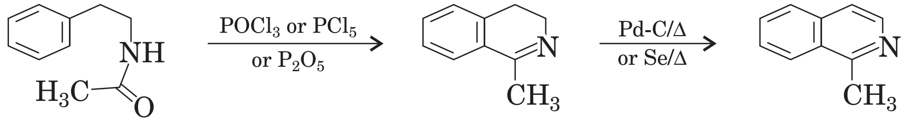
Isoquinoline was first isolated from the quinoline fraction of coal tar. It does not occur free in nature but abundantly in many alkaloids. It is called 2-azanaphthalene or benzo[b] pyridine and is numbered in the same manner as quinoline, but the nitrogen atom is assigned position-2. It is obtained synthetically by employing a number of cyclization procedures.



Isoquinoline

6.4.3.1 Synthetic Methods

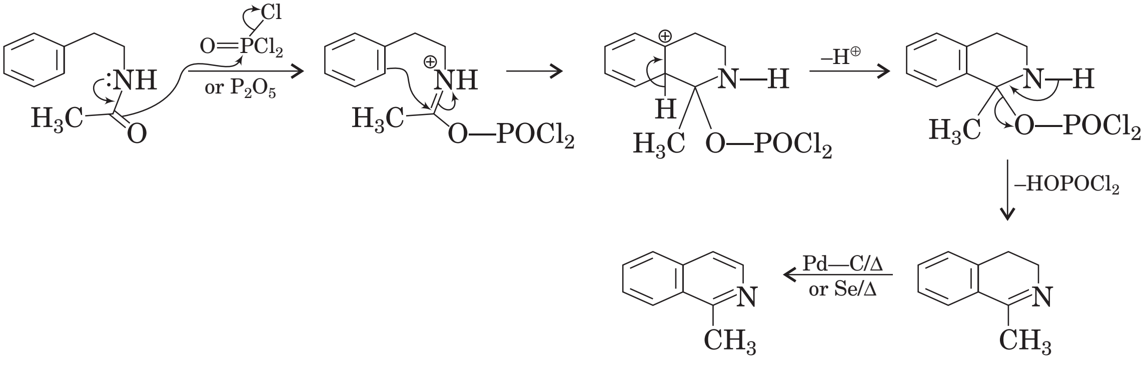
1. The Bischler–Napieralski Synthesis In this method, an acyl derivative of β-phenylethylamine is subjected to cyclodehydration to give a 3,4-dihydroisoquinoline in the presence of phosphoryl chloride, phosphorus pentachloride or phosphorus pentoxide. This is dehydrogenated to isoquinoline by heating with Pd/C or Se. The yields of the products are excellent if electron-donating groups are present in the benzene ring but poor if electron-attracting groups are present. For example:



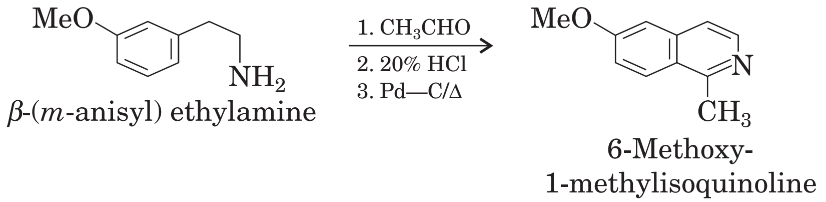
Acetyl derivative of β-phenylethylamine

1-Methylisoquinoline

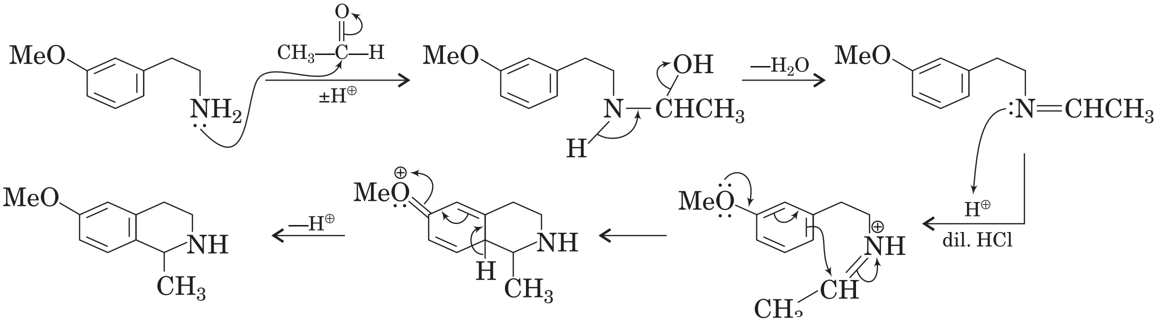
Mechanism of the reaction An intramolecular electrophilic substitution takes place in the presence of acid to give a 3,4-dihydroisoquinoline.



2. The Pictet–Spengler Synthesis In this synthetic process, a β-arylethylamine is condensed with an aldehyde to form an imine, which is then cyclized by treating with dilute hydrochloric acid to give a tetrahydroisoquinoline. It is finally dehydrogenated by heating with Pd-C. For example:

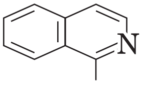


Mechanism of the reaction



Synthesis of an isoquinoline derivative (Target Molecule) through Disconnection Approach

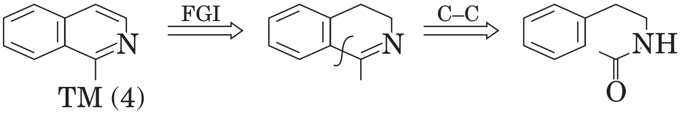
Example:



TM (4)

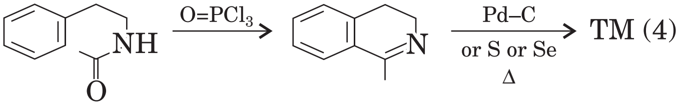
(1-Methylisoquinoline)

Retrosynthetic analysis



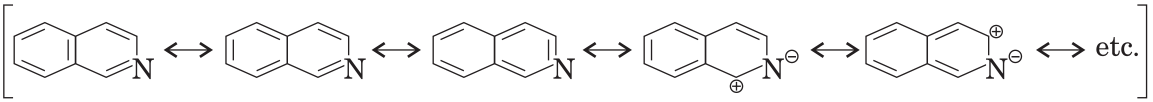
N-(β-phenylethyl)acetamide reacts with $POCl_3$, P_2O_5 or PCl_5 to give isoquinoline after dehydrogenation. The reaction is called *Bischler-Napieralski* reaction.

Synthesis



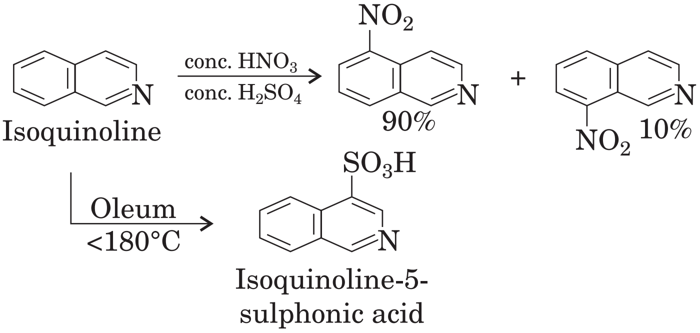
6.4.3.2 Properties and Reactions

Isoquinoline is a colourless liquid having b.p. 243°C. Its smell is similar to that of benzaldehyde. Like quinoline, isoquinoline is also an aromatic compound and is considered to be a resonance hybrid of the following structures.

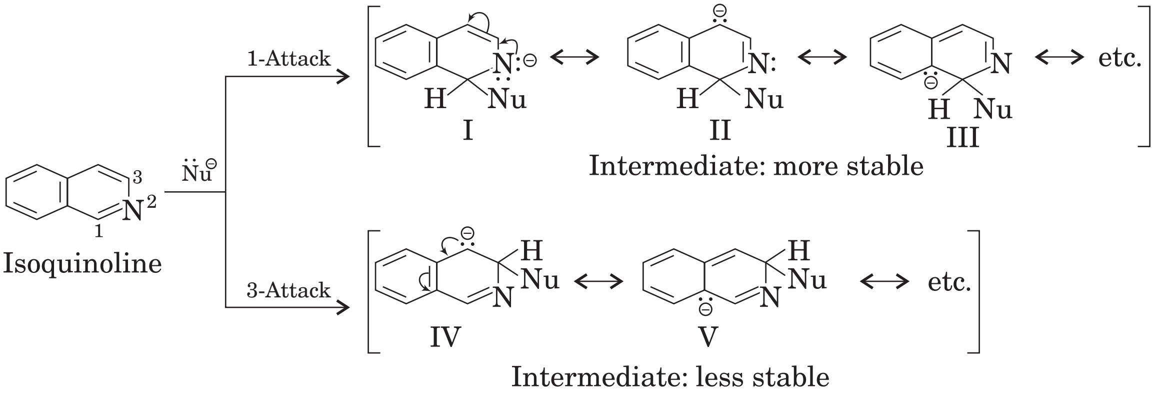


This compound functions as a weak base. It resembles 2-nitronaphthalene in many of its properties. Its dipole moment is 2.6 D.

1. Electrophilic substitution Isoquinoline, like quinoline also undergoes electrophilic substitution preferably in the benzene ring (since benzene ring is more electron rich than the pyridine ring). Electrophilic attack occurs at the 5-(predominantly) and 8-positions. This is because the more stable pyridine ring is being preserved on electrophilic substitution at 5- and 8-positions. Moreover, a few reactions also occur at 4-position (e.g., bromination and mercuration).

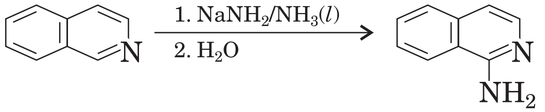


2. Nucleophilic substitution Isoquinoline undergoes nucleophilic substitution usually at C-1 rather than at C-3. The intermediate anions expected for nucleophilic attack at C-1 and C-3 of isoquinoline are as follows:

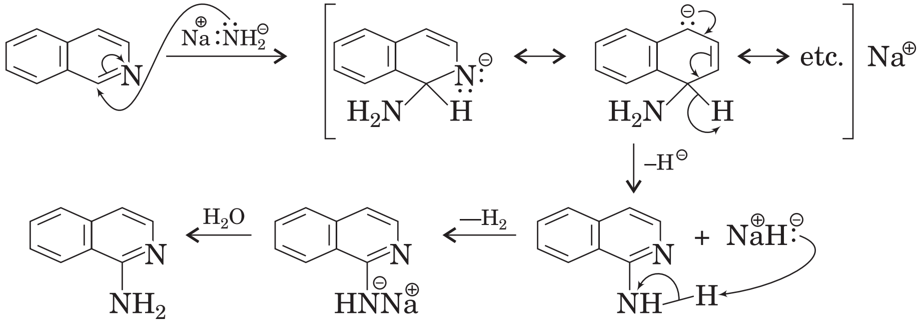


The intermediate anion for 1-attack contains two resonance structures (I and II) is which the aromaticity of the benzene ring is preserved. Also, in one of them the negative charge is accommodated by the electronegative nitrogen atom. The intermediate for 3-attack contains only one such structure (IV) and the negative charge in it is placed on the less electronegative carbon atom. The intermediate for 1-attack is, therefore, relatively more stable than the intermediate for 3-attack. For this reason, isoquinoline undergoes nucleophilic substitution usually at C-1 rather than at C-3.

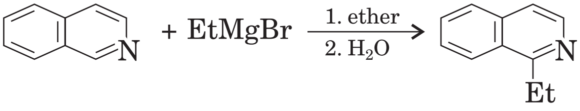
(i)



Mechanism of the reaction

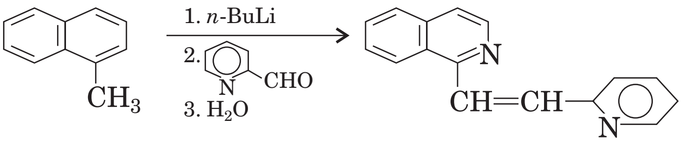


(ii) Organometallic compounds react similarly to give 1-alkyl derivatives. For example:

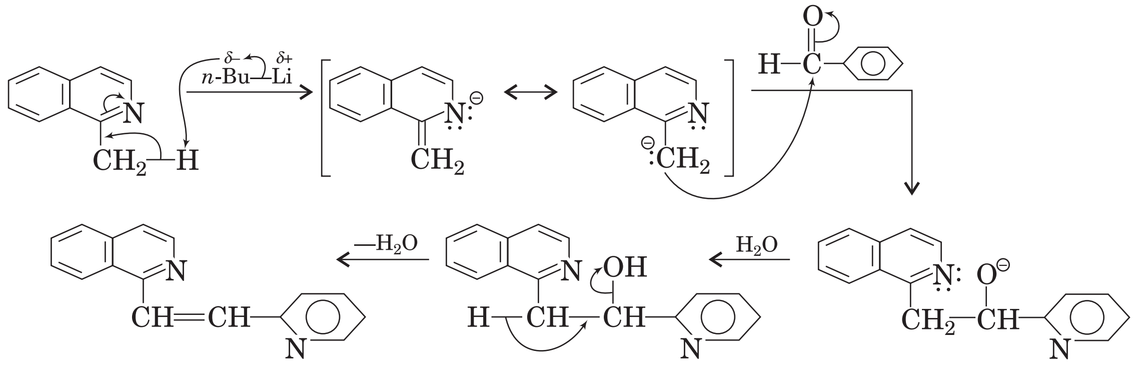


1-Ethylisoquinoline

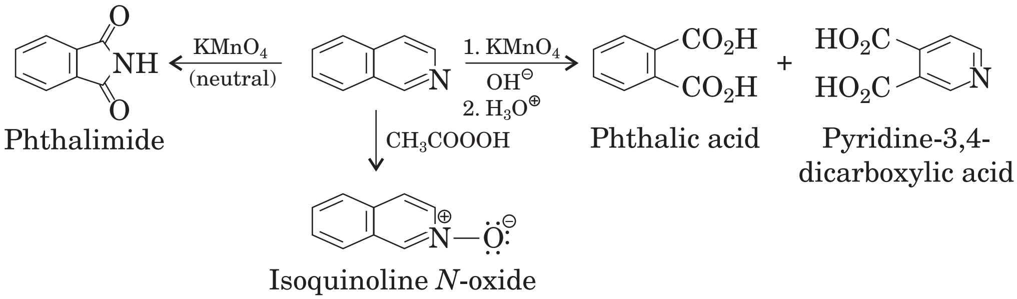
3. Side chain reactivity The alkyl group situated *ortho* to the ring nitrogen displays acidic character because the conjugate base is stabilized by electron delocalization. Hence, such compound condenses with carbonyl compounds. For example:



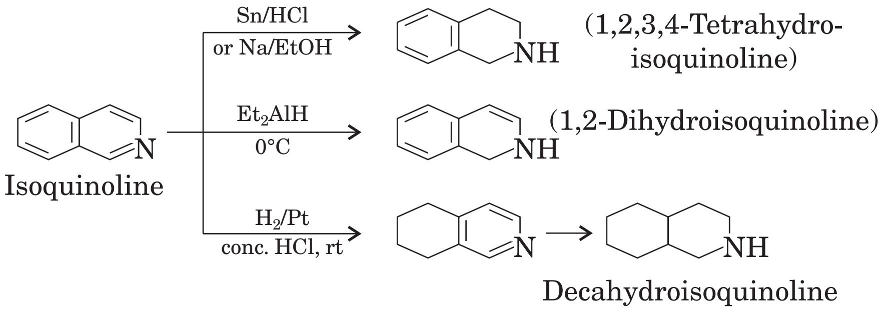
Mechanism of the reaction



4. Oxidation Oxidation of isoquinoline can be effected with $KMnO_4$ (alkaline or neutral) and with peracids.



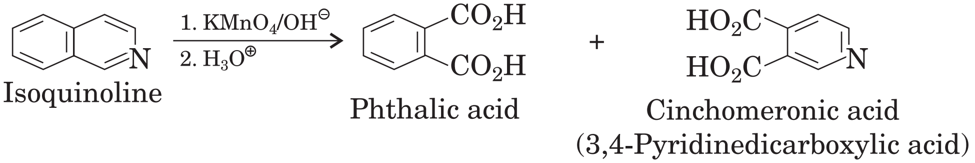
5. Reduction Reduction of isoquinoline gives products depending on the reducing agent and the reaction conditions.



SOLVED PROBLEMS

1. **How would you prove that isoquinoline is a fused ring system involving benzene and pyridine, and it is, in fact, 3,4-benzopyridine?**

Solution When isoquinoline is oxidized with alkaline permanganate, phthalic acid and cinchomeronic acid (3,4-pyridinedicarboxylic acid) are obtained. The formation of two side chains both in the benzene ring and pyridine ring prove that isoquinoline is a fused ring system involving benzene and pyridine.



Isoquinoline

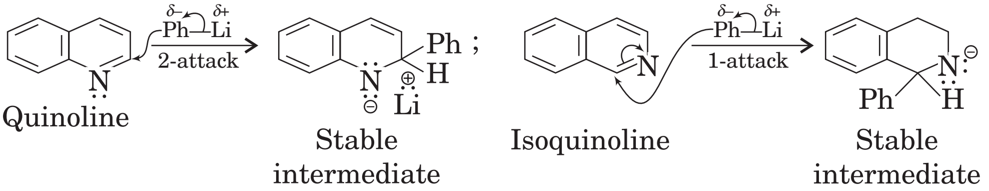
Phthalic acid

Cinchomeronic acid
(3,4-Pyridinedicarboxylic acid)

Formation of 3,4-pyridinedicarboxylic acid also suggest that isoquinoline is 3,4-benzopyridine.

2. **Quinoline on treatment with phenyllithium produces 2-phenylquinoline, whereas isoquinoline on similar treatment produces 1-phenylisoquinoline — explain.**

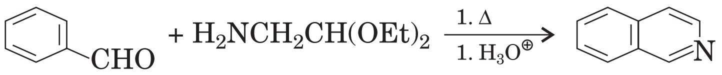
Solution In both the substrates, the nucleophilic attack by $Ph^{\ominus}$ occurs in the activated heterocyclic ring. Attack occurs at C-2 of quinoline because that leads to the formation of a stable intermediate in which the negative charge is accommodated by the electronegative N atom and at the same time the aromaticity of the benzene ring is preserved. Because of the same basic reason, attack in isoquinoline occurs at 1-position. Therefore, quinoline on treatment with PhLi produces 2-phenylquinoline and isoquinoline on similar treatment produces 1-phenylisoquinoline.



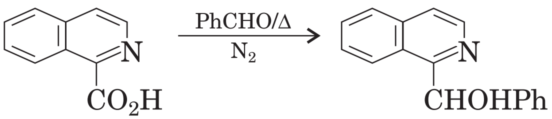
[It is to be noted that C-4 of quinoline is relatively less positive and there is a possibility of *peri*-steric hindrance. For these reasons, attack at C-4, which gives similar stable intermediate, does not take place normally.]

3. **Suggest a mechanism for each of the following reactions:**

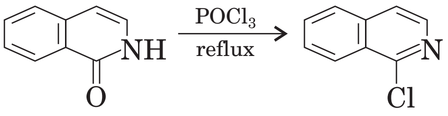
(a)



(b)

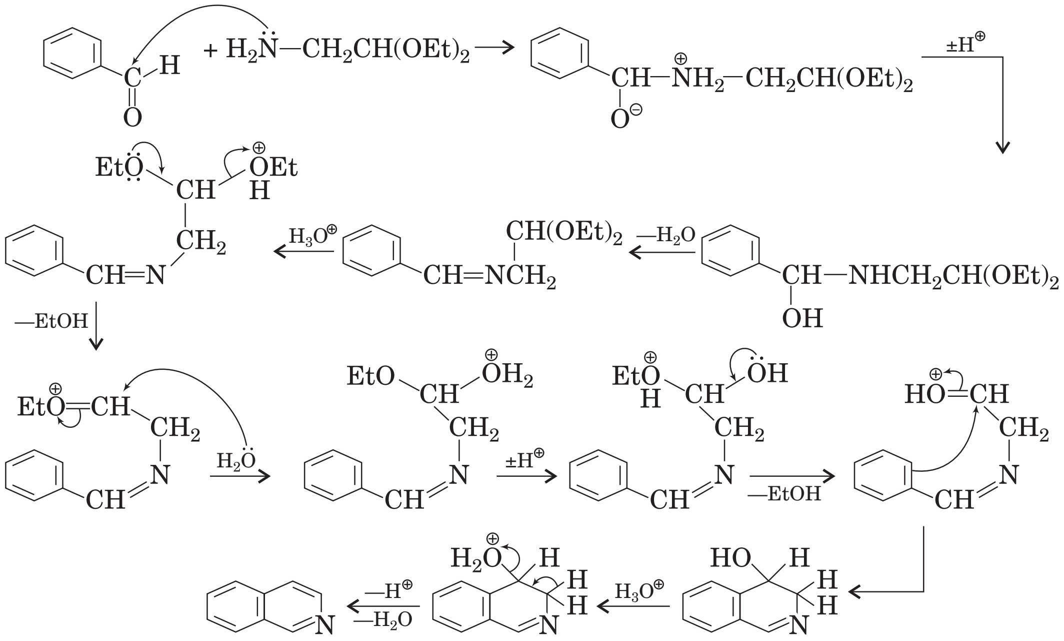


(c)



Solution

(a)



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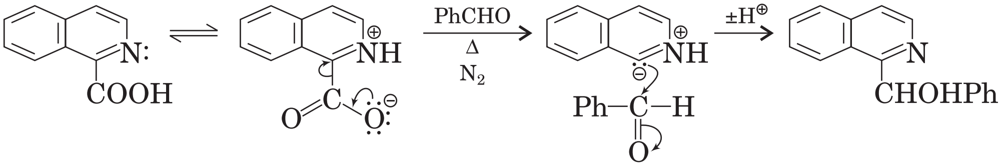

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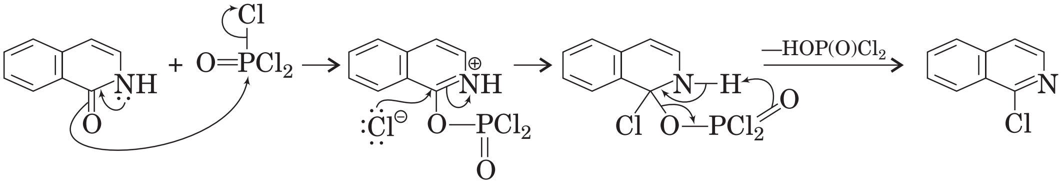
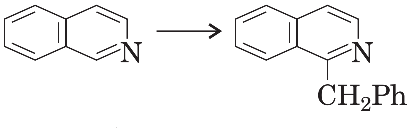
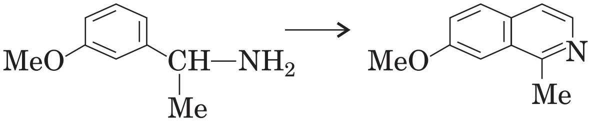


4. How would you carry out the following transformations?

(a)



(b)



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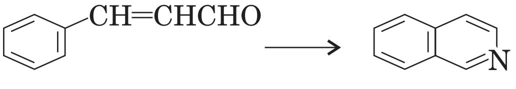
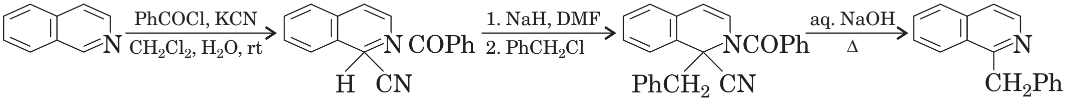
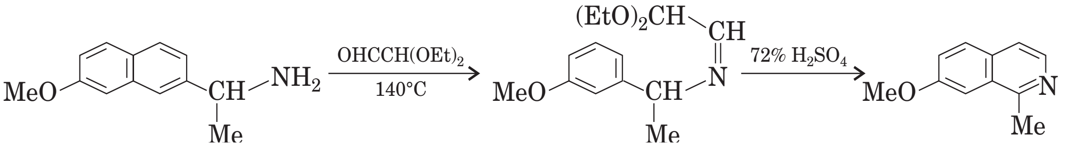


Solution

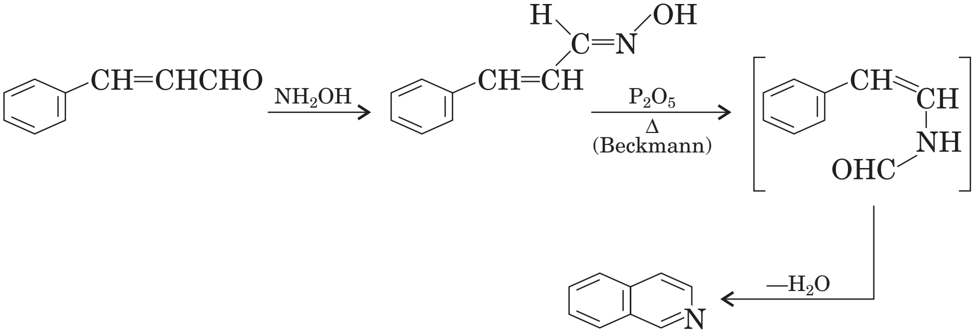
(a)



(b)

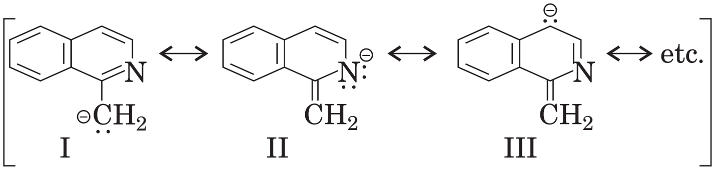


(c)

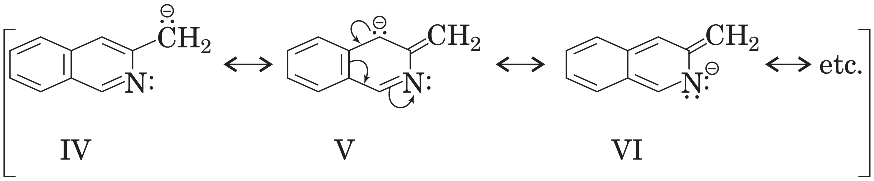


5. **How would you prepare 1-methylisoquinoline by the Bischler–Napieralski synthesis? [C.U. 2012]**
   [**Hint:** See **article no. 6.4.3.1.**]
6. **1-Methylisoquinoline condenses with benzaldehyde much readily than 3-methylisoquinoline. Explain.**

Solution The conjugate bases of 1- and 3-methylisoquinoline may be represented as follows:



Conjugate base of 1-methylisoquinoline

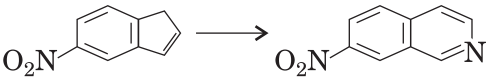


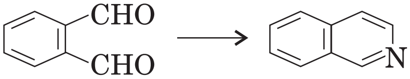
Conjugate base of 3-methylisoquinoline

The conjugate base of 1-methylisoquinoline contains three canonicals (I–III) in which the aromaticity of the benzene ring is preserved. Also, in one of them, the negative charge is placed on electronegative N atom. This structure is relatively more stable. The conjugate base of 3-methylisoquinoline, on the other hand, contains only two canonicals with aromatic benzene ring and in none of them the negative charge is placed on nitrogen. Therefore, the conjugate base of 1-methylisoquinoline is relatively more stable and is formed rapidly. Because of this, 1-methylisoquinoline condenses with benzaldehyde much rapidly as compared to 3-methylisoquinoline.

STUDY PROBLEMS

1. How would you carry out the following transformations?

(a)


(b)


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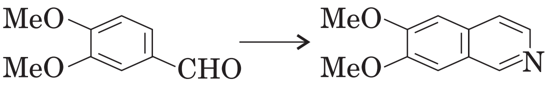
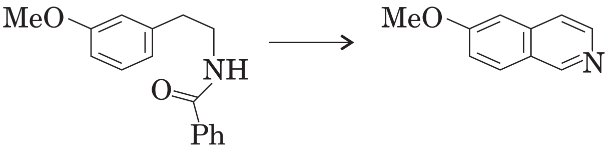
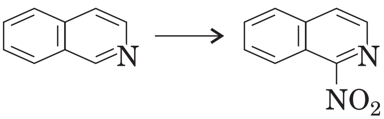
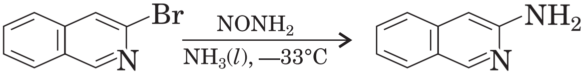


(d)


(e)


2. Prepare a curved-arrow mechanism for each of the following reactions:

(a)


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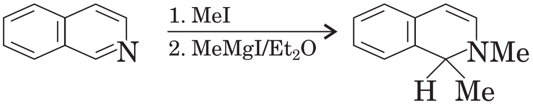

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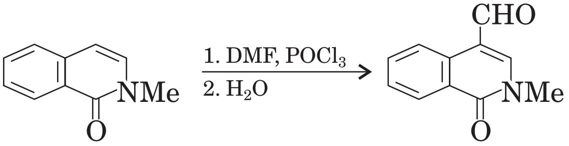

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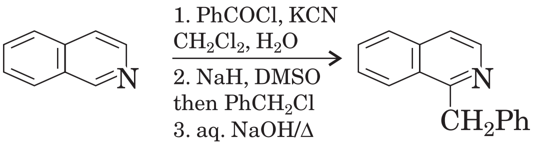
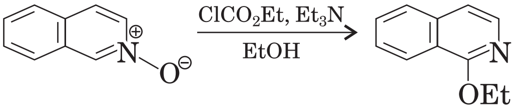


(e)



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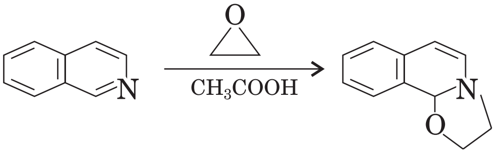
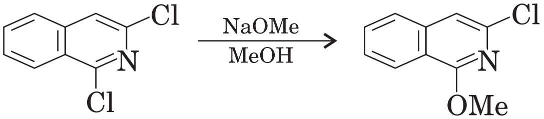


(g)



3. At which positions do quinoline and isoquinoline react most readily with nucleophiles? Give your reasoning.

4. At which positions do quinoline and isoquinoline react most readily with radicals and why?

5. At which positions do quinoline and isoquinoline undergo nitration and why?

6. Write down the most stable tautomers of 1-, 4- and 8-oxyisoquinolines.

7. Predict the structures of the mono-nitration product (major) expected to be obtained from (i) 1-benzylisoquinoline and (ii) 7-methoxyisoquinoline.

8. Write structure of the product obtained when 1,3-dichloroisoquinoline is allowed to react with NaCH $(CO_2Et)_2$.

9. What happens when 1-methylisoquinoline is treated with benzaldehyde in the presence of alkali? **[C.U. 2011]**
[**Hint:** See **article no. 6.4.3.2**]

References

1. Meyers, A. I. *Heterocycles in Organic Synthesis*; Wiley: New York, 1974.
2. Paquette, L. A. *Principles of Modern Heterocyclic Chemistry*; W. A. Benjamin: New York, 1968.
3. Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon: Elmsford, New York, 1968.
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5. Bansal, R. K. *Heterocyclic Chemistry*, 5th ed.; New Age.
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Stereochemistry of Alicyclic Compounds

7

Chapter Outline

Introduction

7.1 Conformational Analysis of Cyclohexanes
- 7.1.1 Concept of Ring Strain: Relative Stabilities of Cycloalkanes
- 7.1.2 Ring Size and Ease of Cyclization
- 7.1.3 Conformations of Cyclohexane and Substituted Cyclohexanes

7.2 Conformation and Reactivity in Cyclohexanes
- 7.2.1 Steric Effect
- 7.2.2 Stereoelectronic Effect
- 7.2.3 Reactions of Cyclohexane Derivatives

INTRODUCTION

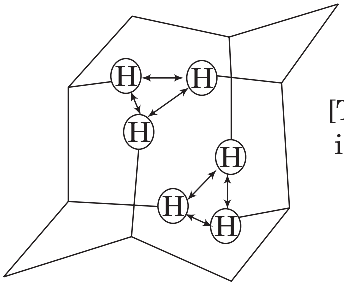
The stereochemistry of acyclic systems has already been discussed but the relation between the conformation and reactivity of carbocyclic systems deserves special attention. Cyclohexane is the most important carbocyclic ring system on which stereochemical studies have been done extensively leading to important conclusions. Because of this, a few aspects of conformation and reactivity of cyclohexane and its derivatives are to be discussed in this chapter. Due to well-defined conformation of cyclohexane, the influence of conformation on reactivity is most easily studied. Most of the reactions of simple cyclohexane derivatives are expected to involve a single chair conformation, provided the inversion of one chair form to another is restricted by a sufficient large substituent (*holding* or *anchoring group*) like *t*-butyl group in suitable position. The differences in reactivity of axial versus equatorial susbstituents in chair conformation of cyclohexane may be well understood by considering some common reactions. Reactions of cyclohexane involving boat or twist-boat conformations do not take place frequently and are known only in some special cases.

7.1 CONFORMATIONAL ANALYSIS OF CYCLOHEXANES

Conformation is the spatial arrangement of atoms in a molecule that can be converted into another spatial arrangement by rotation about the single bond or twisting of bonds. The assessment of the relative thermodynamic stabilities, reactivities and physical properties of different conformations of a molecular entity is known as *conformational analysis*. Before going to discuss about the conformational analysis of cyclohexane, we have to discuss ring strain and *Baeyer strain theory*.

7.1.1 Concept of Ring Strain: Relative Stabilities of Cycloalkanes

Cycloalkanes (alkanes that contain rings of carbon atom) do not all have the same relative stability. From a number of experimental observations it has been suggested that cyclohexane is the most stable cycloalkane and that, in comparison, cyclopropane and cyclobutane are much less stable. This difference in relative stability is due to what is called *ring strains*. The factors which influence the ring strain of cycloalkanes are angle strain (or Baeyer strain), eclipsing (torsional) strain resulting from eclipsing of adjacent pairs of C—H bonds, *butane-gauche* interactions and transannular (across the ring) strain arising from steric repulsion between the H atoms on opposite sides of the ring. However, the last one is a source of strain in medium rings (C_7—C_{12}).



[Transannular interactions in cyclodecane ($C_{10}H_{22}$)]

Cyclobutane is found to be less reactive than cyclopropane, while cyclopentane and higher homologues are found to be much less reactive than these two. In order to account for the above behaviour of three- and four-membered ring compounds *vis-a-vis* higher cycloalkanes Adolf von Baeyer proposed a theory which is known as *Baeyer strain theory*.

The main assumptions of Baeyer strain theory, which is based on a purely mechanical concept of bonding, are as follows:

(i) When bond angles deviate from the normal tetrahedral value (109°28′), a strain is set up in the molecule.

(ii) All of the carbon atoms constituting a cycloalkane ring exist in the same plane. Thus, a cyclopropane ring is an *equilateral triangle*, a cyclobutane ring is a *square* and other cycloalkane rings are *regular polygons*.

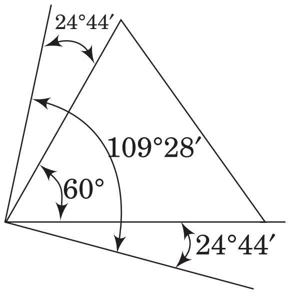
(iii) When these molecules assume the above-mentioned shapes, there occurs deviation from the normal tetrahedral angle which causes a lot of strain in the molecule. This strain, commonly referred to as *angle strain* (sometimes called Baeyer strain) depends upon the extent of such deviation. The greater the deviation of bond angle from the normal tetrahedral value (109°28′), the greater is the strain and consequently, less stable (or more reactive) is the ring. However, the sign of deviation does not make any difference.

(iv) Bond angle strain is expressed in terms of deviation of angle d, according to the following relationship:

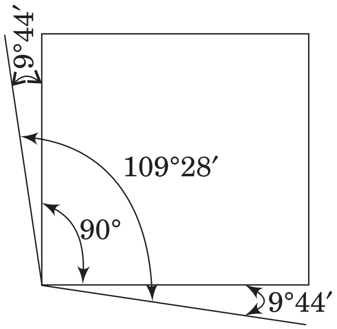
$$d = \frac{1}{2}(109°28' – \text{value of the C—C—C angle of the planar ring})$$

(In the above expression, the factor $\frac{1}{2}$ is put because the distortion of bond angle has been assumed to be equally shared between the two bonds.)

Baeyer worked out the deviation from normal bond angle or what is called angle strain in various cycloalkanes. Cyclopropane, for instance, has C—C—C bond angles of 60° (the internal angle of an equilateral triangle). This implies that the normal tetrahedral angle of 109°28′ between any two bonds is compressed to 60°, and that each of the two bonds involved is pulled by $\frac{1}{2}(109°28' – 60°) = 24°44'$. This value actually represents the angle strain in cyclopropane. Similarly, the C—C—C angle in cyclobutane would be 90° because each of the four carbons is situated at the corner of a square. Thus, the angle strain in cyclobutane is $\frac{1}{2}(109°28' – 90°) = 9°44'$.

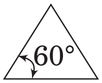
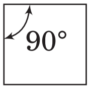
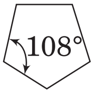
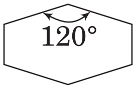
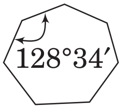
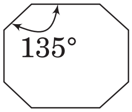


Angle of deviation in cyclopropane



Angle of deviation in cyclobutane

The angle strain for cycloalkanes calculated for various ring sizes are displayed in the following table.

	Cycloalkane and its geometry	C—C—C angle in planar ring	Angle strain
1.	Cyclopropane (equilateral triangle)		$\frac{1}{2}(109°28' - 60°) = +24°44'$
2.	Cyclobutane (square planar)		$\frac{1}{2}(109°28' - 90°) = +9°44'$
3.	Cyclopentane (regular pentagon)		$\frac{1}{2}(109°28' - 108°) = +0°44'$
4.	Cyclohexane (regular hexagon)		$\frac{1}{2}(109°28' - 120°) = -5°16'$
5.	Cycloheptane (regular heptagon)		$\frac{1}{2}(109°28' - 128°34') = -9°33'$
6.	Cyclooctane (regular octagon)		$\frac{1}{2}(109°28' - 135°) = -12°46'$

It becomes clear from the above data that angle strain decreases from cyclopropane to cyclopentane. Therefore, according to Baeyer strain theory, cyclopropane should be the least stable cycloalkane and stability should increase gradually from cyclopropane to cyclopentane. This is actually found to be so. Cyclopropane undergoes ring-opening reactions easily; cyclobutane undergoes ring-opening reactions under drastic conditions and cyclopentane does not undergo ring-opening reactions.

Limitations of Baeyer Strain theory According to Baeyer strain theory, cyclohexane and the higher cycloalkanes are expected to be increasingly unstable and hence more reactive. Contrary to this prediction, cyclohexane and the higher homologues are found to be quite stable. They do not undergo ring-opening reactions. Instead they resemble open-chain alkanes in reactivity, i.e., they undergo substitution reaction. The higher cycloalkanes, as predicted by the strain theory, are not actually planar; they actually assume puckered conformation to minimize their strain. Thus, Baeyer strain theory satisfactorily accounts for the reactivity of cyclopropane, cyclobutane and cyclopentane, but it is not at all applicable to cyclohexane and the higher cycloalkanes.

7.1.1.1 Calculation of Ring Strain for Cycloalkanes on the Basis of their Heats of Combustion and Comparison of their Stabilities

The heat of combustion of a compound is the amount of heat released when a compound is burned in the presence of excess of oxygen, i.e., the heat of combustion of a compound is, in fact, the enthalpy change for the complete oxidation of the compound.

The general equation for the combustion of a cycloalkane can be represented as follows:

$$\underset{\text{Cycloalkane}}{(CH_2)_n} + \frac{3}{2}nO_2 \rightarrow nCO_2 + nH_2O + \text{heat (heat of combustion)}$$

Since cycloalkanes are not isomeric, therefore, their heats of combustion cannot be compared directly. However, the amount of heat evolved per CH_2 group can be calculated and on this basis, the amounts of ring strain can be calculated and the stabilities of cycloalkanes can be compared.

The heats of combustion of some cycloalkanes are given in the following table.

Cycloalkanes, $(CH_2)_n$	n	Heat of combustion (kcal/mol)	Heat of combustion per CH_2 group (kcal/mol)
Cyclopropane	3	499.8	166.6
Cyclobutane	4	655.9	164.0
Cyclopentane	5	793.5	158.7
Cyclohexane	6	944.5	157.4
Cycloheptane	7	1108.2	158.3
Cyclooctane	8	1269.2	158.6
Cyclononane	9	1429.4	158.8
Cyclodecane	10	1586.0	158.6
Cyclopentadecane	15	2362.5	157.5
Unbranched alkane			157.4

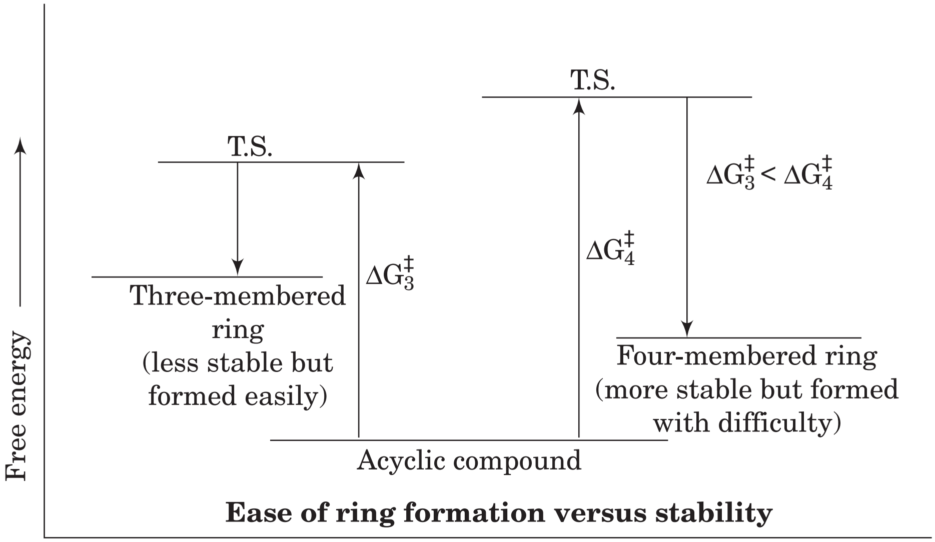
Cyclohexane has the lowest heat of combustion per CH_2 group (157.4 kcal/mol). This amount is same as that of an unstrained long-chain alkane. Therefore, it can be assumed that cyclohexane has no ring strain and that it can serve as the standard for comparison with other cycloalkanes. Ring strain for other cycloalkanes can be calculated by multiplying 157.4 kcal/mol by n and then subtracting the result from the heat of combustion of the cycloalkane. Thus, the amounts of ring strain of cycloalkanes $(CH_2)_n$, where $n = 3$ to 10 are 27.6, 26.4, 6.5, 0, 6.4, 10.0, 12.9 and 12.0 kcal/mol respectively. The more the ring strain a molecule possesses, the more potential energy it has and less stable it is compared to its ring homologue. Therefore, cyclopropane having the greatest amount of ring strain is the least stable cycloalkane. Cyclobutane possessing the second largest amount of ring strain is somewhat more stable than cyclopropane. Cyclopentane and cycloheptane possessing the same modest amount of ring strain are more stable than cyclobutane. Eight, nine and ten-membered rings having slightly larger amounts of ring strain are somewhat less stable than cycloheptane. The amount of ring strain then falls off with consequent increase in stability.

Cycloalkanes can be classified by size and ring strain as follows:

(i) Small rings (C_3 and C_4) having large ring strain
(ii) Common ring (C_5 and C_6) having little or no ring strain
(iii) Medium ring (C_7 to C_{13}) having little ring strain
(iv) Large rings ($\geq C_{14}$) having no ring strain

7.1.2 Ring Size and Ease of Cyclization

The ease of ring formation and the stability of the resulting ring do not run parallel. The stability of the ring formed is not always reflected by the scale of activation energy and this is because some other factors are found to be involved. The most important fact in the ring formation from an acyclic system is to bring the two ends of the molecule together (within a bonding distance) and statistically the probability is increased with decreasing size of the ring and vice versa. It, thus, follows that the entropy of activation plays an important role. The larger the size of the ring to be made the greater would be the value of entropy of activation. Therefore, from the entropy point of view, smaller rings are easy to be formed compared to larger rings. The entropies of ring formation of a few smaller rings such as cyclopropane, cyclobutane, cyclopentane and cyclohexane are –32.2, –45.6, –55.6 and –88.7 $\text{J mol}^{-1}\,\text{K}^{-1}$, respectively. Due to greater rigidity of cyclohexane, a sharp drop in entropy value compared to more flexible cyclopentane has been observed. An idea about the ease of ring formation versus ring stability (taking three- and four-membered rings as examples) can be obtained from the following energy diagram.

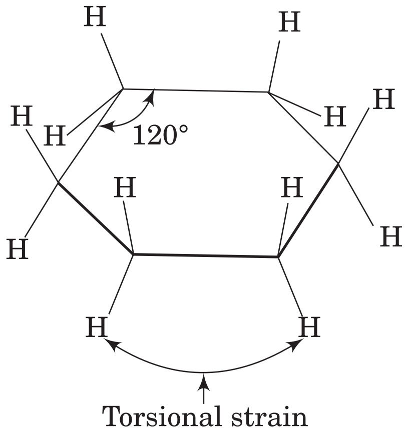


Ease of ring formation versus stability

Stability of a ring depends on the strain factors involved. This factor favours the formation of five- and six-membered rings more than that of three- and four-membered rings. Strain factor becomes unfavourable (more effective as destabilising force) as the ring-size becomes seven, eight and nine and then again favourable for larger rings. Due to considerable decrease in strain factor, five-membered rings are easily formed from the acyclic system compared to six-membered ring. Six-membered ring is almost strainless but, due to entropy factor, its rate of formation is slower.

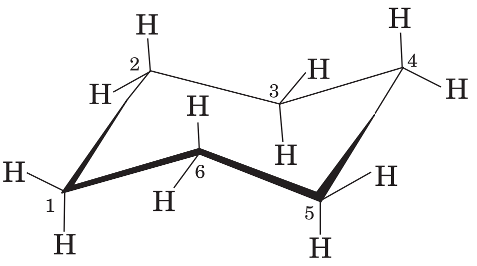
7.1.3 Conformations of Cyclohexane and Substituted Cyclohexanes

If the carbon of a cyclohexane ring were placed at the corners of a regular planar hexagon, all the C—C—C bond angles would have to be 120°. Because the expected normal C—C—C bond angle should be near the tetrahedral value of 109°28′, the suggested planar shape of cyclohexane would have angle strain at each of the carbons and would correspond to less stable cyclohexane molecules than those with normal bond angles. Angle strain is not the whole story with regard to the instability of the planar form. A planar ring would also have torsional or eclipsing strain because the bonds on adjacent CH_2 groups would be eclipsed.

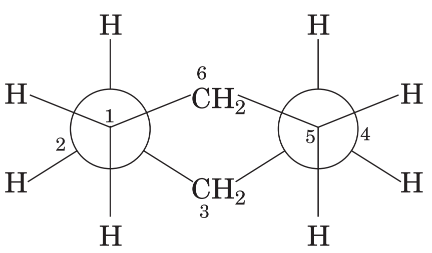


Strained planar form of cyclohexane with eclipsed carbons and hydrogens

Since cyclohexane is a very stable cycloalkane, it must have no angle strain and no torsional strain. This can only happen if cyclohexane can assume a nonplanar conformation. In fact, cyclohexane overcomes these strains by being puckered to give a conformation that is almost completely free of strain. This conformation is called *chair conformation*. With C—C—C bond angles of 111°05′ (close to normal tetrahedral value of 109°28′), the chair conformation is nearly free of angle strain. Again, all the C—H bonds are staggered (the dihederal angle is 56° instead of 60°) making it free of torsional strain as well. The staggered arrangement of bonds in the chair conformation becomes apparent in the Newman projection. Furthermore, the distance between the H atom on one carbon and that on another carbon of the chair form (249–251 pm) being greater than twice the van der Waals radii of hydrogen. Thus, there is no non-bonded interaction, i.e., van der Waals (steric) strain in the cyclohexane chair.



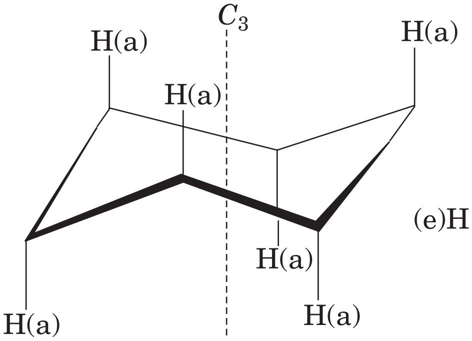
Chair conformation of cyclohexane



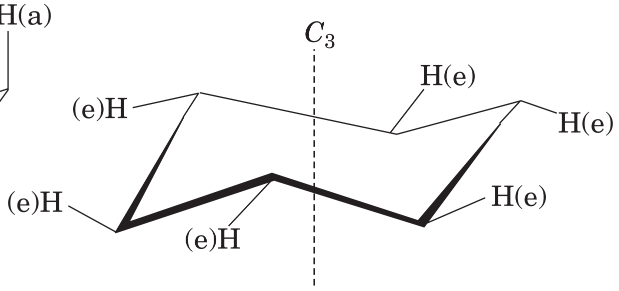
Newman projection of the chair conformation (all bonds are staggered)

7.1.3.1 Axial and equatorial bonds

In the chair conformation of cyclohexane, all the 12 C—H bonds are not equivalent; there are two sets of six bonds. In one set, the six C—H bonds are parallel to the C_3 axis (three- fold simple axis of symmetry) or S_6 axis (six-fold alternating axis of symmetry) of the cyclohexane molecule or perpendicular to the horizontal plane containing any three alternate carbon atoms of the ring. These are called *axial* bonds and are symbolised as 'a'. Three of these axial bonds are directed upward and the other three downward. They should all be vertically aligned and alternate up and down all round the ring. The axial bond of the upcarbon points upward, while the axial bond of the down carbon points downward. In the other set, the six C—H bonds are distributed around the periphery (equator) of the ring making an angle of 109°28′ with the C_3 axis or ±19°28′ with the horizontal plane containing any three alternate carbon atoms of the ring. These are called *equatorial* bonds and are symbolised as 'e'. Three of these are directed upward and the other three downward. Each carbon has an axial and an equatorial bond.

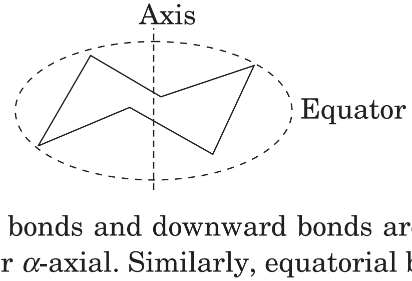


Axial bonds
(parallel to C_3)



Equatorial bonds
(make an angle of
109°28′ with C_3)

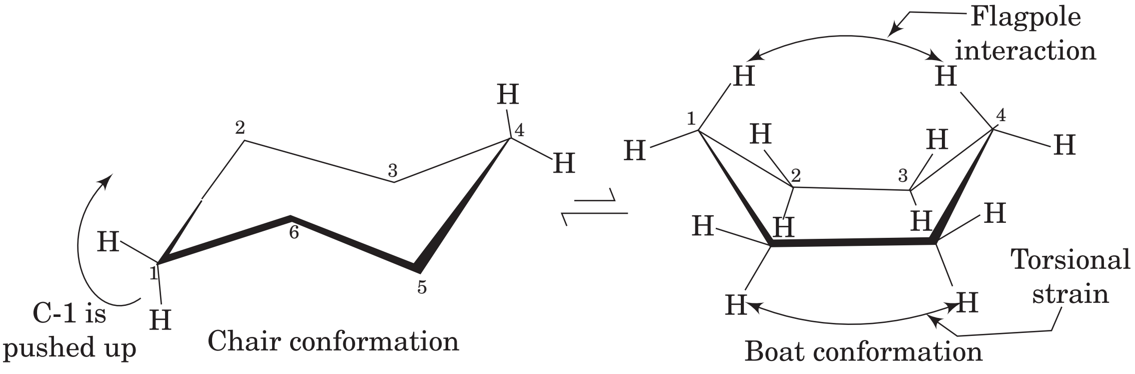
The axial bonds are so designated because they are directed vertically, parallel to the axis of the ring and the equatorial bonds are so designated because they are directed outward, toward the equator of the ring.



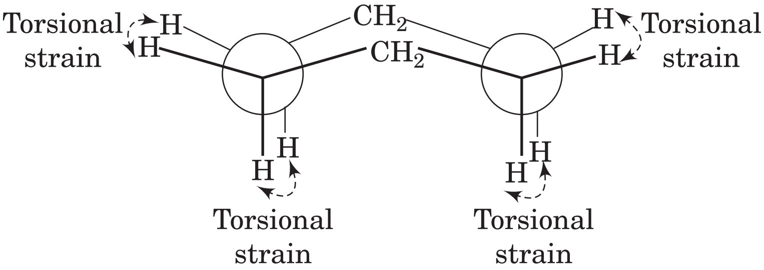
Upward bonds are called 'β' bonds and downward bonds are called 'α' bonds. Therefore, axial bonds may be β-axial or α-axial. Similarly, equatorial bonds are classified as α or β, when projected downward and upward, respectively.

7.1.3.2 Boat Conformation of Cyclohexane

By partial rotations about the carbon—carbon single bonds of the ring, the chair conformation can assume another shape called *boat conformation*. In fact, the boat conformation of cyclohexane can be formed by 'flipping' one end of the chair conformation up (or down). This may be shown as follows:



A Newman projection of the boat conformation of cyclohexane may be given as follows:

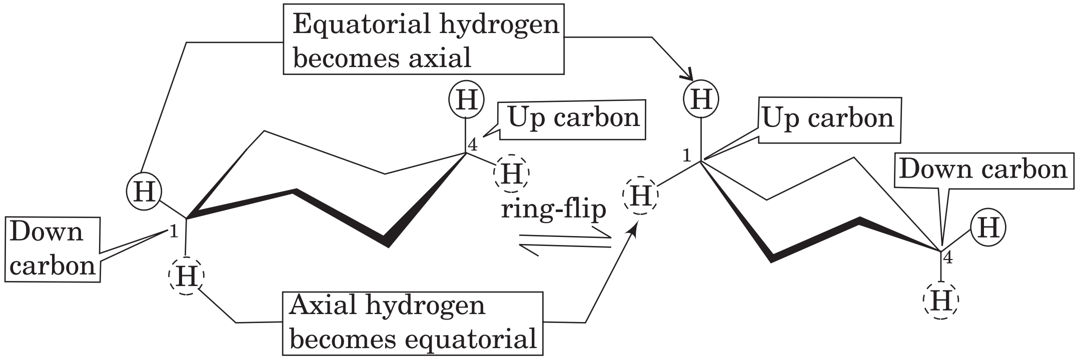


Newman projection of the boat conformation

Like the chair conformation, the boat conformation of cyclohexane is free of angle strain. However, the boat conformation is not free of torsional strain because there is eclipsing of two pairs of hydrogens on each set of gunwall carbons (C-2, C-3 and C-5, C-6). Again, the two flagpole hydrogens (the hydrogens which point upward from the ends of the boat like two flagpoles) on C-1 and C-4 are close enough to each other (which are within 180 pm, less than twice the van der Waals radius of hydrogen, i.e., $120 \times 2 = 240$ pm) to cause van der Waals repulsion (steric strain). This steric interaction is called 'flagpole' interaction. Torsional strain and flagpole interactions cause the boat conformation to have considerable higher energy (6.5 kcal mol^{-1}) than the chair conformation.

7.1.3.3 The Ring Inversion (Flipping) of Cyclohexane

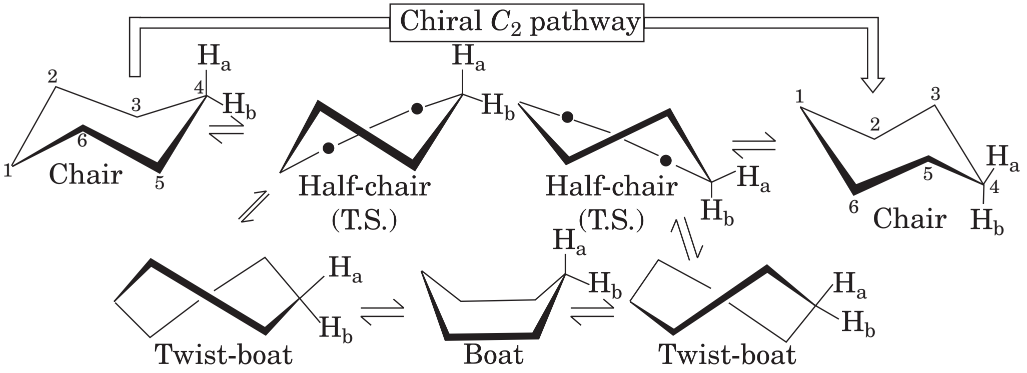
Because of the ease of rotation about the C—C single bonds, cyclohexane rapidly interconvert between two stable chair conformations. This interconversion is known as ring-flip or ring-inversion. When interconversion between two chair conformation occurs, the equatorial bonds become axial and vice versa (or equatorial hydrogen becomes axial and vice versa) but directions of the bonds remain unaffected, i.e., α-bonds remain α (below the plane) and β-bonds remain β (above the plane). In addition, up and down carbons become down and up carbon, respectively.

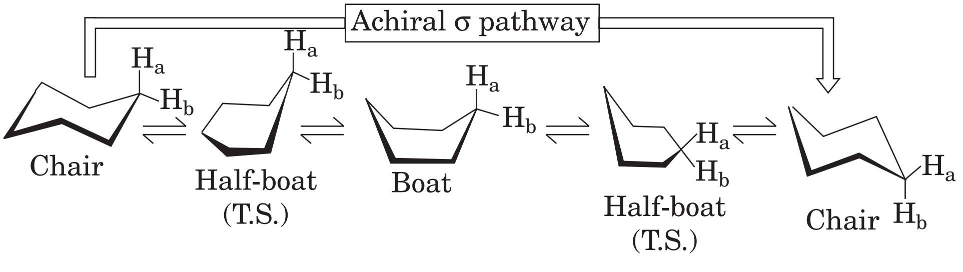

Equatorial hydrogen becomes axial
H
Up carbon
4
H
ring-flip
H
Down carbon
1
H
Axial hydrogen becomes equatorial
H
1
H
Up carbon
Down carbon
H
4
H

[Since the activation energy for the process of ring inversion at room temperature is very low (10.8 kcal/mol), the rate of ring inversion or chair-chair interconversion is very fast (~ 10^5 times/s) at room temperature. The interconversion can be arrested by cooling cyclohexane to very low temperature (≃100°C). When the NMR spectrum of cyclohexane is run at low temperature, two signals are obtained. This indicates two different sorts of protons (axial and equatorial).]

This type of *homomeric* transformation of one chair form of cyclohexane into another equivalent chair form has been given the general name *topomerisation*. Since axial and equatorial hydrogens of two equivalent chair conformations are diastereotopic in stereochemical relation, the ring inversion of cyclohexane is specifically called *diastereotopomerization*.

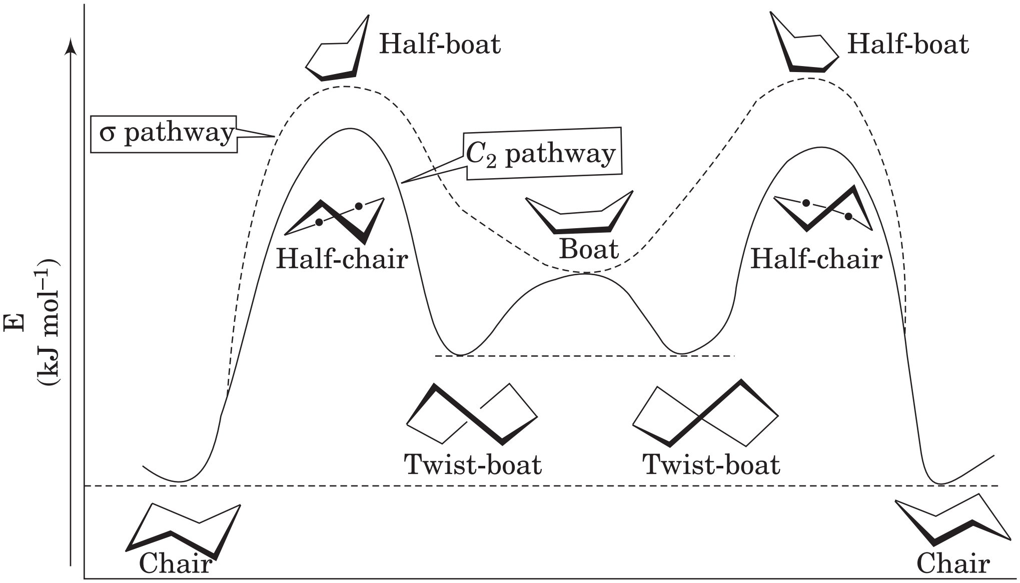
Two different pathways (chiral C_2 pathway and achiral σ pathway) have been considered for ring inversion of cyclohexane chair form and these can be shown as follows:





C_2 pathway The chair conformer may be twisted to get the half-chair conformation (transition state) in which the four carbon atoms lie in a plane and the other two alternately above and below the plane. There occurs extensive bond angle deformation accompanied with an increase in torsional strain. The half-chair conformation has a C_2 axis but no σ plane. Further change leads to the twist-boat conformation which has no angle strain but suffers from some torsional strain. It corresponds to an energy minimum and is actually a conformer. It leads to the true boat conformation. The boat conformation in its turn can go back to the original chair or to the inverted chair with equal facility through the enantiomeric twist-boat and half-chair conformations, respectively. This pathway is called the C_2 pathway, since the C_2 axis of the ground state chair form is retained along the pathway.

σ pathway The chair form on twisting produces an envelope-like half-boat conformation (transition state) with five of the carbon atoms in a plane and the sixth one either above or below it. This conformation has a σ plane and so is achiral. It leads directly to an energy minimum conformation which is the true boat. The boat conformation in its turn can go back to the original chair or to the inverted chair equally well through the equivalent half-boat conformation. This pathway is called a σ pathway, since both the half-boat and the classical or true boat conformations retain the symmetry plane of chair ground state.

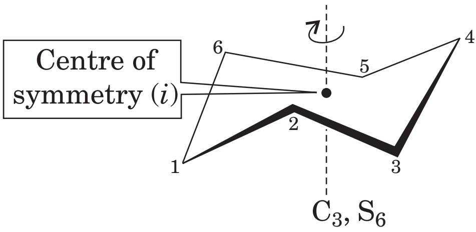


Inversion coordinate

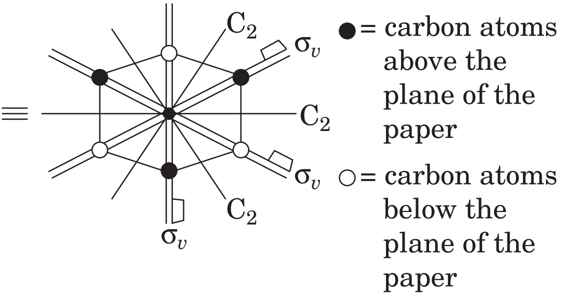
Because of the greater stability of the chair, >99% of the molecules are estimated to be in a chair conformation at any given moment.

7.1.3.4 Symmetry Elements in Chair and Boat Conformations

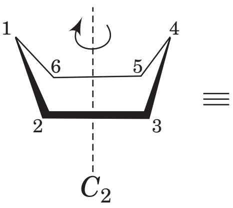
The chair conformation of cyclohexane has a three-fold simple axis of symmetry (C_3 axis) and a six-fold alternating axis of symmetry (S_6 axis). The vertical axis which passes through the centre of the chair is a C_3 as well as an S_6 axis. In addition, there are three two-fold simple axis of symmetry (C_2 axis) each of which bisects two opposite bonds, a centre of symmetry (i), and three vertical plane of symmetry (σ_v) passing through diagonal carbon atoms and four H atoms.



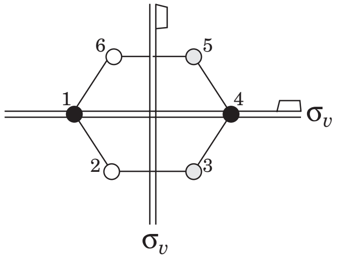
Chair conformation of cyclohexane


≡
C_2
σ_v
C_2
σ_v
C_2
σ_v
● = carbon atoms above the plane of the paper
○ = carbon atoms below the plane of the paper

The boat conformation of cyclohexane has a two-fold simple axis of symmetry (C_2 axis) passing through the centre of the boat and two vertical planes of symmetry (σ_v) one of which is bisecting C-2—C-3 and C-5—C-6 bonds and the other is passing through C-1 and C-4.

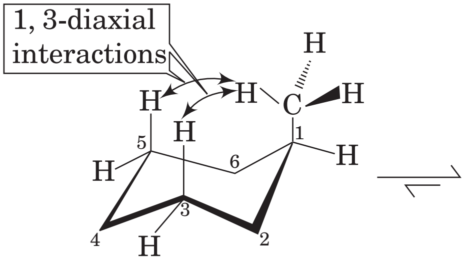


Boat conformation of cyclohexane



7.1.3.5 *Conformational Analysis of Methylcyclohexane*

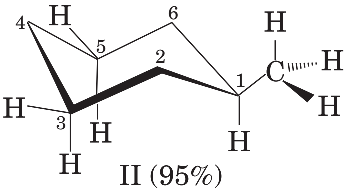
Methylcyclohexane has two possible chair conformations (I and II), and these are interconvertible through the bond rotations that constitute a ring-flip. In conformation I, the methyl group occupies an *axial* position, while in conformation II, the methyl group occupies an *equatorial* position.



I (5%)

Axial-methyl conformation of methylcyclohexane (less stable)

⇌



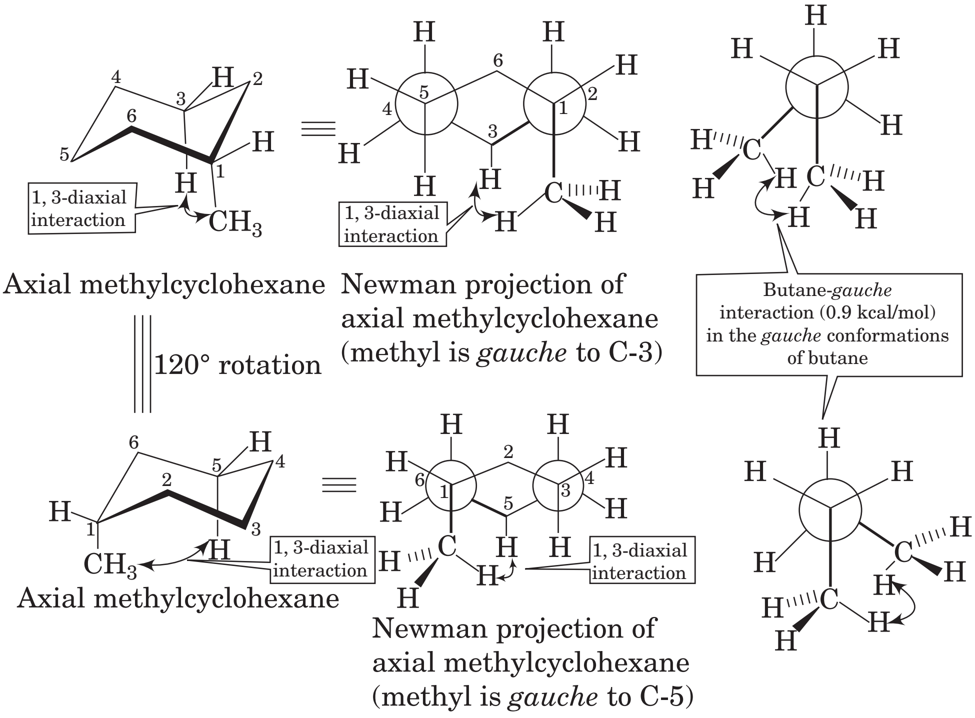
II (95%)

Equatorial-methyl conformation of methylcyclohexane (more stable)

Studies suggest that the conformation II with the equatorial methyl group is more stable than the conformation I with the axial methyl group by about 1.8 kcal/mol. Thus, in the equilibrium mixture, the conformation with the methyl group in the equatorial position is the predominant one, constituting about 95% of the equilibrium mixture.

An axial methyl group in methylcyclohexane has one of its hydrogens within 190–200 pm of the axial hydrogens at C-3 and C-5 (*syn*-axial hydrogens). This distance is less than the sum of van der Waals radii of two hydrogens (240 pm) and causes van der Waals strain in the axial conformation. This type of steric strain, because it arises from an interaction between an axial group on carbon atom 1 and an axial hydrogen on carbon atom 3 (or 5), is called a 1,3-diaxial interaction. This is also called *syn-axial interaction*.

The greater stability of methylcyclohexane with an equatorial methyl group and the strain caused by a 1,3-diaxial interaction is the same as the strain caused by the close proximity of the hydrogen atoms of methyl groups in the *gauche* form of butane can be well understood through an inspection of molecular models and Newman projections of the two conformations. If we make a model of the conformation of methylcyclohexane with axial methyl and hold it so that we can sight along the C-1—C-2 bond, we see that the methyl group and C-3 of the ring have the same relative positions as the two methyl groups in the *gauche* conformation of butane. This can be shown by a Newman projection. If we now sight along the C-1—C-6 bond, we see similar arrangement but with C-5 taking the place of C-3. The two butane-*gauche* interactions are shown separately as follows:



Axial methylcyclohexane

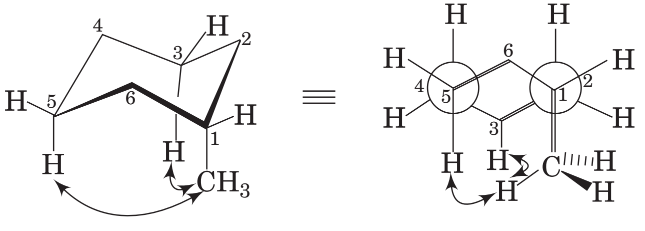
Newman projection of axial methylcyclohexane (methyl is *gauche* to C-3)

Butane-*gauche* interaction (0.9 kcal/mol) in the *gauche* conformations of butane

Axial methylcyclohexane

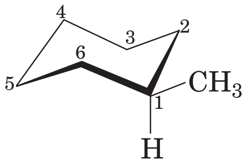
Newman projection of axial methylcyclohexane (methyl is *gauche* to C-5)

Both of these interactions may be shown in a single figure as follows:



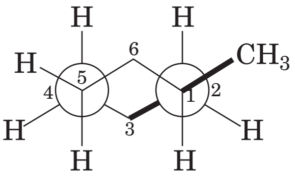
(Two butane-*gauche* interactions in
axial methylcyclohexane)

If we make a model of equatorial methylcyclohexane, and sight along the C-1—C-2 bond, we see that the methyl group and C-3 of the ring have the same relative locations as the two methyl groups in the *anti* conformation of butane. This can be well demonstrated by a Newman projection. Again, if we sight along the C-1—C-6 bond, we see that methyl and C-3 are *anti* to each other.

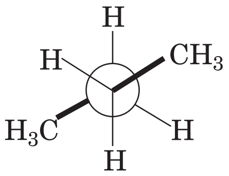


Equatorial
methylcyclohexane

≡

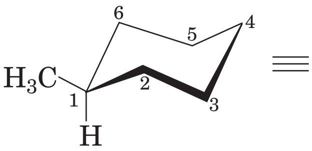


Newman projection of
equatorial methylcyclohexane
(methyl is *anti* to C-3)



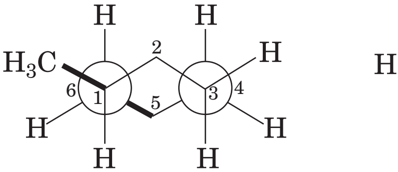
anti conformation
of butane with
no steric interaction

120° rotation

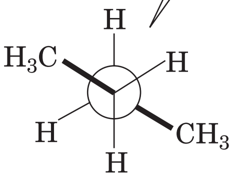


Equatorial
methylcyclohexane

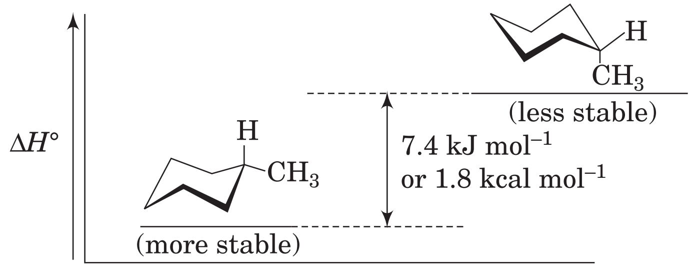
≡



Newman projection of
equatorial methylcyclohexane
(methyl is *anti* to C-5)



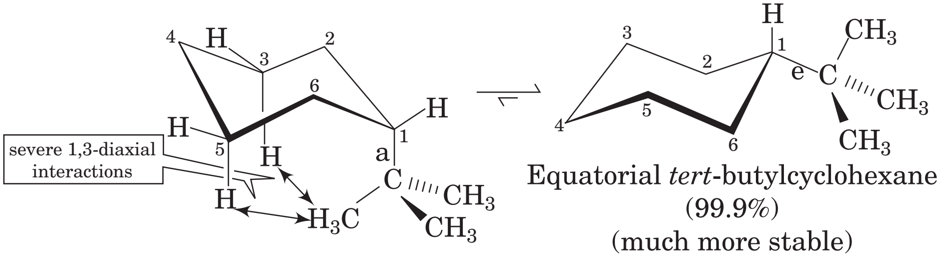
Thus, for each 1,3-diaxial methyl-hydrogen interaction there is a butane-*gauche* interaction involving the methyl group and a carbon atom of the ring. For each butane-*gauche* interaction, the energy of the system increases by an amount of 0.9 kcal/mol. The axial conformation of methylcyclohexane has two butane-*gauche* interactions, whereas the equatorial conformation has no such interaction. Therefore, the axial conformation is higher in energy by 0.9 × 2 or 1.8 kcal/mol than the equatorial conformation. In fact, this value is in good agreement with the experimental value of 1.7 kcal/mol.



Relative enthalpies of axial and equatorial methyl cyclohexane

7.1.3.6 Conformational Analysis of tert-butylcylohexane

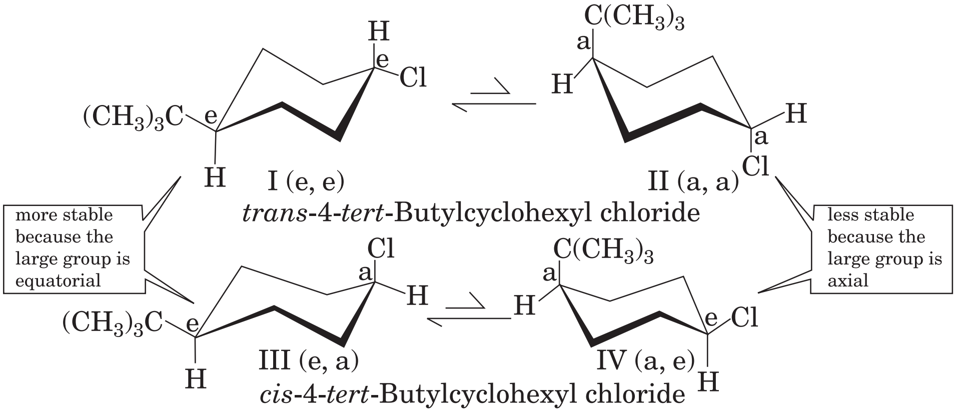
The relative amounts of the two chair conformers depend on the bulk of the substituent. The substituent with greater bulk will have greater preference for equatorial position because it will have stronger 1,3-diaxial interactions. Since the *tert*-butyl group is much larger than a methyl group, the 1,3-diaxial interactions are even more destabilising. For this reason, *tert*-butylcyclohexane exists nearly exclusively (99.9%) in equatorial chair conformation. The equatorial conformation is favoured over the axial conformation by about 20 kJ mol^{-1} (about 5 kcal mol^{-1}). The relative energy costs of placing the methyl and *tert*-butyl groups in an axial position are thus in direct relation to their sizes.



Axial *tert*-butylcyclohexane (0.1%)
(much less stable)

Equatorial *tert*-butylcyclohexane
(99.9%)
(much more stable)

Holding group The *tert*-butyl group is characterized as a 'holding group' because its own tendency to be in the equatorial position holds a smaller substituent axial or equatorial, depending on whether it is *cis* or *trans*. 4-*tert*-Butylcyclohexyl chloride, for example, could exist in four chair conformations I, II, III and IV.


(CH3)3C
C(CH3)3
H
Cl
e
a
more stable because the large group is equatorial
less stable because the large group is axial

I (e, e)
II (a, a)
trans-4-*tert*-Butylcyclohexyl chloride

III (e, a)
IV (a, e)
cis-4-*tert*-Butylcyclohexyl chloride

Conformations I and II have the substituents *trans* to one another, but in I they are both equatorial, whereas in II they both are axial. Conformations III and IV have the substituents in the *cis*-relationship, with the *tert*-butyl and chlorine equatorial and axial, respectively, in III, and the reverse in IV. A *tert*-butyl (group is very large and bulky compared to chlorine and considerable steric strain results when *tert*-butyl is axial. For this reason, I and III with *tert*-butyl equatorial are much more favourable than II and IV. That is, in the *cis*-isomer the *tert*-butyl group holds smaller chlorine atom axial and in the *trans*-isomer, it holds the smaller chlorine atom equatorial.

A bulky group which makes the molecule conformationally biased is called an 'anchoring group'. A conformationally biased molecule is called 'anancomeric'.

[The conformation with an axial *tert*-butyl group is so little that chemists say sometimes that the conformational equilibrium is 'locked'. This statement is somewhat misleading because it implies that the two conformations are not at equilibrium. The equilibrium actually occurs rapidly, but simply contains very little of the conformation with the *tert*-butyl group axial.]

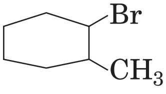
Conformational free energies (kJ mol^{-1}) of a few substituents in substituted cyclohexanes

Substituent	$\Delta G°$	Substituent	$\Delta G°$
—CH_3	7.1	—OC_2H_5	3.8
—C_2H_5	7.3	—NO_2	4.6
—CMe_3	24	—OTs	2.1
—Ph	11		
—C≡CH	2.1	—NHCOPh	6.4
—C≡N	1.06	—SH	3.8
—COOH	5.9	—F	1.05–1.75
—CO_2Et	5.3	—Cl	2.10–2.68
—OAc	1.5	—Br	2.01–2.10
—OCH_3	2.5	—I	1.97–2.55

7.1.3.6 Cis-trans Isomerism, Stereochemical Consequences of Ring-flip, and Conformational Analysis of Disubstituted Cyclohexanes

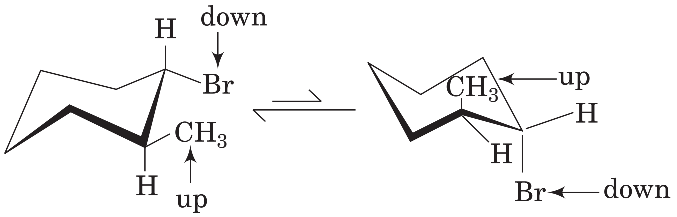
1. *Cis-trans* isomerism

Let us consider a typical disubstituted cyclohexane, 1-bromo-2-methylcyclohexane.



1-Bromo-2-methylcyclohexane

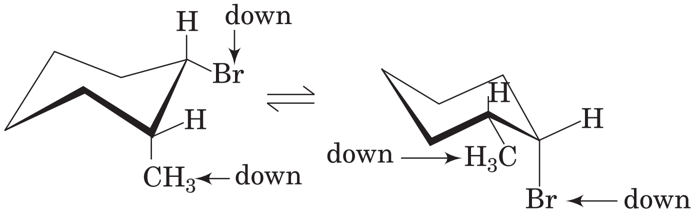
In *trans* stereoisomer of this compound, both the bromo and methyl groups assume equatorial positions. The compound remains in rapid equilibrium with a conformational diastereoisomer in which both the bromo and methyl groups assume axial positions.



trans-1-Bromo-2-methylcyclohexane

Either conformation is called *trans*-1-bromo-2-methylcyclohexane. The stereochemical designation *trans* is used with cyclic compounds when the two substituents have an up-down relationship. It is to be noted that the up-down relationship is not affected by the conformational equilibrium.

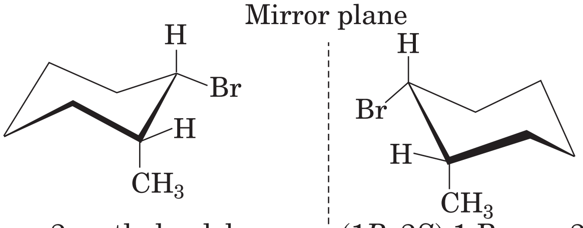
In *cis* stereoisomer of 1-bromo-2-methylcyclohexane, the bromo and methyl groups occupy adjacent equatorial and axial positions. This compound is also a rapidly equilibrating mixture of two conformational diastereoisomers. In a *cis*-disubstituted cycloalkane, the substituents have an up-up or a down-down relationship. The *cis* relationship is not altered by the conformational equilibrium.



cis-1-Bromo-2-methylcyclohexane

The same definition of *cis* and *trans* substitution can be applied to substituent groups also in 1,3- and 1,4-positions of a cyclohexane ring.

It is to be noted that when the substituents in a disubstituted cyclohexane are on chiral carbons, the designations *cis* and *trans* indicate the relative stereochemical configurations of the two clinical carbons, but they say nothing about the absolute configurations of these carbons. Thus, there are two enantiomers of *cis*-1-bromo-2-methylcyclohexane.



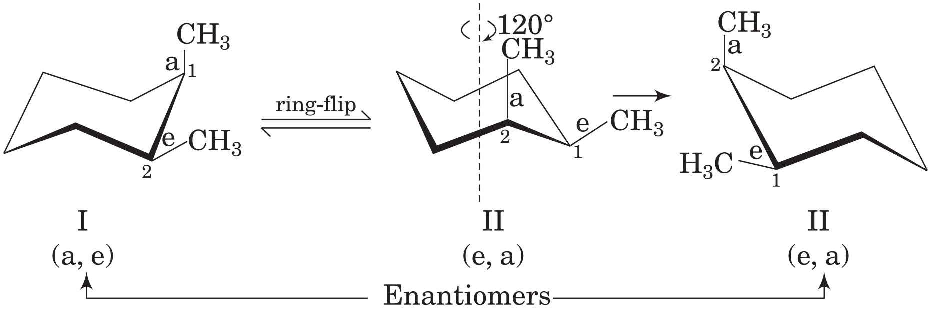
(1*S*, 2*R*)-1-Bromo-2-methylcyclohexane | (1*R*, 2*S*)-1-Bromo-2-methylcyclohexane

Enantiomers of *cis*-1-bromo-2-methylcyclohexane

2. Stereochemical consequences of ring-flip

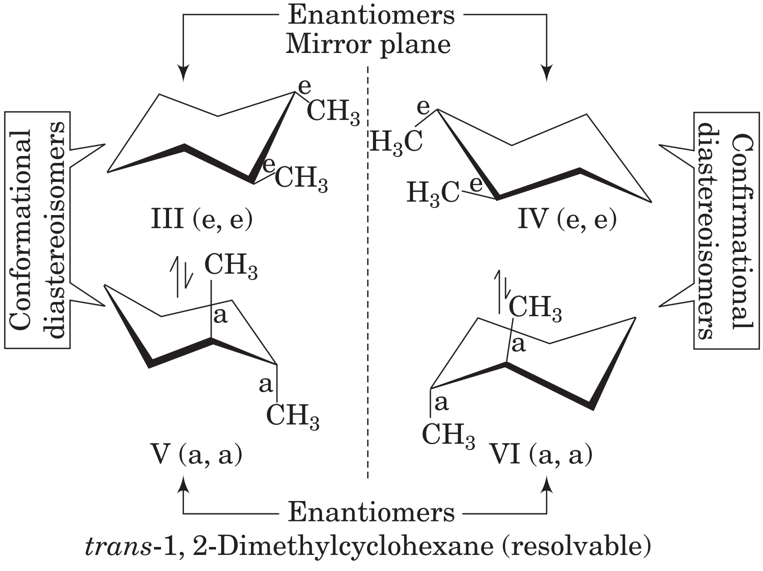
The ring-flip has some interesting stereochemical consequences that can be well illustrated with diastereiosomeric dimethylcyclohexanes. These are *cis-trans* isomers of (i) 1, 2-dimethylcyclohexane, (ii) 1,3-dimethylcyclohexane and (iii) 1,4-dimethylcyclohexane.

(i) *cis*-1,2-Dimethylcyclohexane: It exists in two energetically equivalent chair conformations (I and II) each of which places one methyl group axial and one equatorial, i.e., if one is *axial-equatorial* (a, e), the other is *equatorial-axial* (e, a). These conformations are non-superimposable on their mirror images, i.e., these are chiral. However, they cannot be separated (resolved) because one is the non-superimposable mirror image (conformational enantiomer) of the other (this can be observed by rotating the conformation II by an angle of 120° around a vertical axis) and are interconverted very rapidly (because of low potential energy barrier) by ring-flip at ordinary temperature. Thus, *cis*-1,2-dimethylcyclohexane exists as a nonresolvable *dl*-pair (a racemic mixture) and as a consequence, it cannot be optically active.



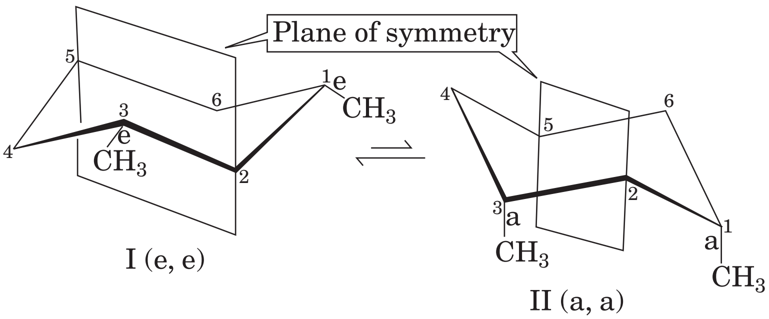
cis-1,2-Dimethylcyclohexane (non-resolvable)

***trans*-1,2-Dimethylcyclohexane:** The compound is chiral and it exists as two enentiomeric forms (III and IV). However, these two enantiomers cannot be interconverted by ring-flip because flipping causes equatorial methyls to become axial methyls. Actually, the ring-flip converts each enantiomer into a conformational diastereoisomer; the (e, e) conformer becomes the (a, a) conformer and vice versa. Because each enantiomer has independent existence, *trans*-1,2-dimethylcyclohexane can be isolated in optically active form (resolvable).



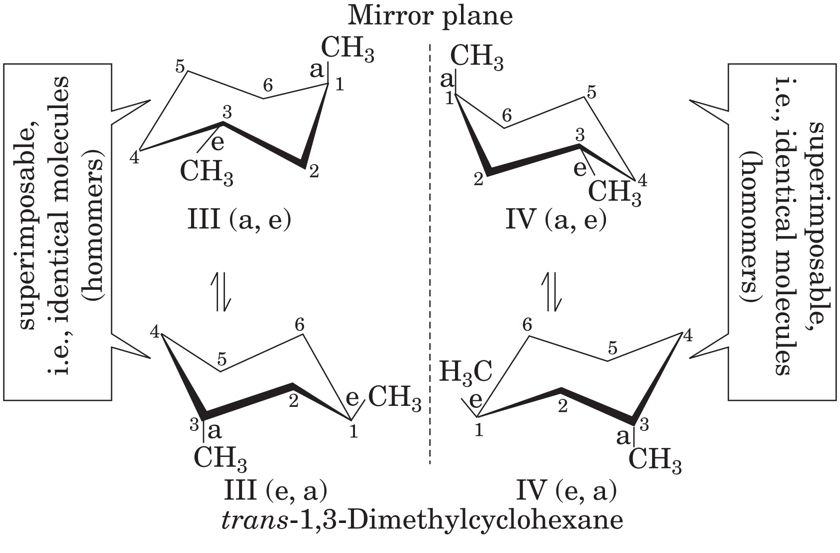
trans-1, 2-Dimethylcyclohexane (resolvable)

(ii) *cis*-1,3-Dimethylcyclohexane: The compound exists in two distinct chair conformations: diaxial (a, a) and diequatorial (e, e). These conformational diastereoisomers (I and II) are interconvertible by chair flip. Although each of these conformations has two asymmetric carbon atoms, neither of them is chiral because each has a plane of symmetry passing through C-2 and C-5, i.e., both conformations are *meso*. *cis*-1, 3-Dimethylcyclohexane is, therefore, a rapidly interconverting mixture of two different *meso* conformations and is optically inactive.



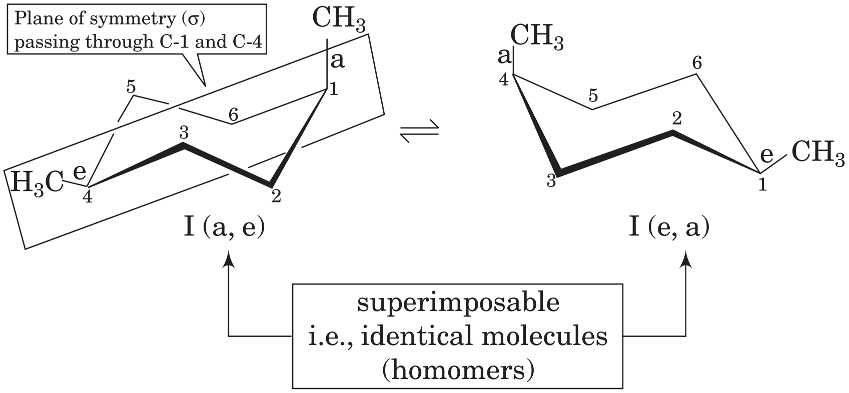
cis-1, 3-Dimethylcyclohexane
(an optically inactive *meso* compound)

***trans*-1,3-Dimethylcyclohexane:** In this compound one methyl group is always equatorial and the other is axial. This is a chiral molecule (non-superimposable on its mirror image) and unlike the case of the *cis*-1,2-compound, flipping the ring converts the molecule , not to its enantiomer, but to a species which is superimposable with the original molecule, i.e, they are homomers (topomers). Thus, in this case, the (+) and (–) forms are capable of discreate existance. Therefore, *trans*-1,3-dimethylcyclohexane can exist as a resolvable *dl*-pair (III and IV), i.e. it can be isolated in optically active form.



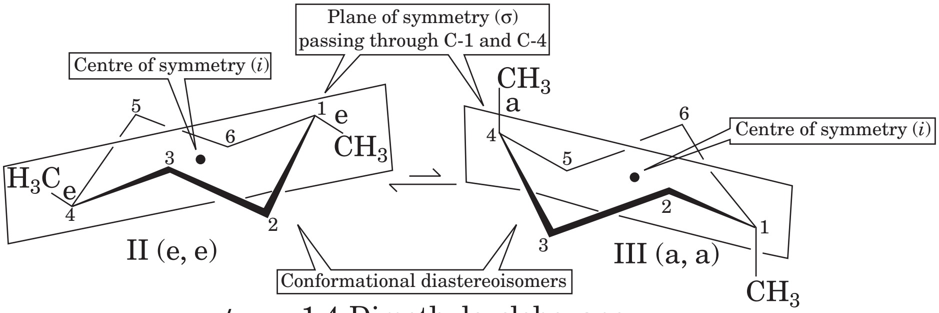
trans-1,3-Dimethylcyclohexane

(iii) *cis*-1,4-Dimethylcyclohexane: In this compound one methyl group is always equatorial and the other is axial. Flipping the ring converts the molecule not to its enantiomer but to a species which is superimposable with the original molecule, i.e, they are homomers (topomers). The molecule has a vertical plane of symmetry passing through C-1 and C-4. Therefore, the compound is achiral and optically inactive.



cis-1, 4-Dimethylcyclohexane
(optically inactive)

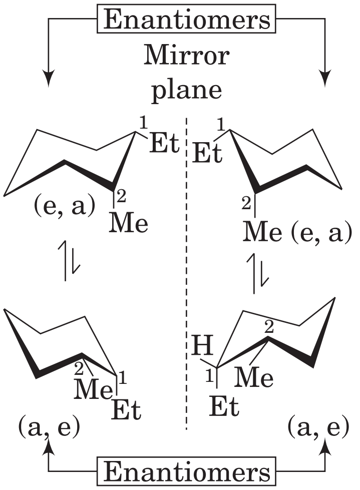
trans-1,4-Dimethylcyclohexane: It exists as two non-equivalent chair conformations: II(e, e) and III (a, a). Both of them have a vertical plane of symmetry passing through C-1 and C-4 and a centre of symmetry. Thus, the compound is achiral and optically inactive.



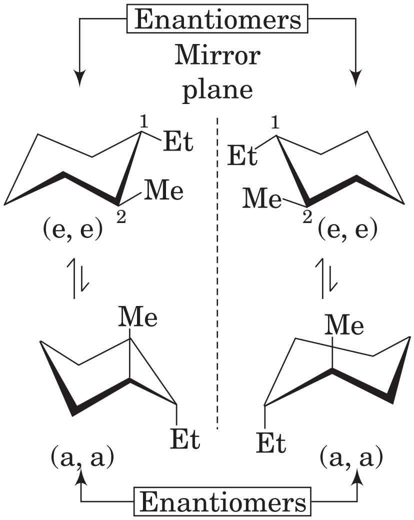
trans-1,4-Dimethylcyclohexane
(optically inactive)

Stereochemistry of disubstituted cyclohexanes when the two substituents are different

1. 1,2-Disubstituted cyclohexane When the two substituents in a 1,2-disubstituted cyclohexane are different (e.g., 1-ethyl-2-methylcyclohexane), both *cis* as well as *trans* isomers are resolvable. The *trans*-isomer exists in the preferred diequatorial (e,e) conformation while the *cis*-isomer in equatorial-axial (e, a) conformation with the bulkier group predominantly equatorial.

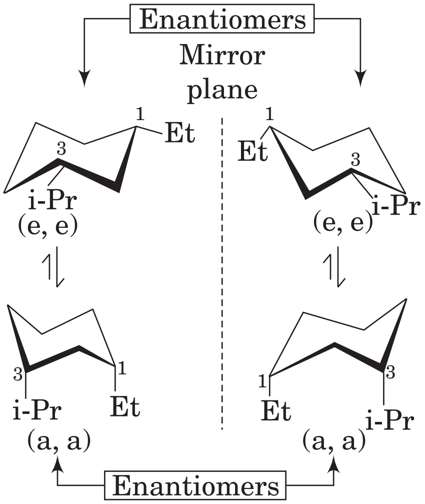


cis-1-Ethyl-2-methylcyclohexane
(resolvable)

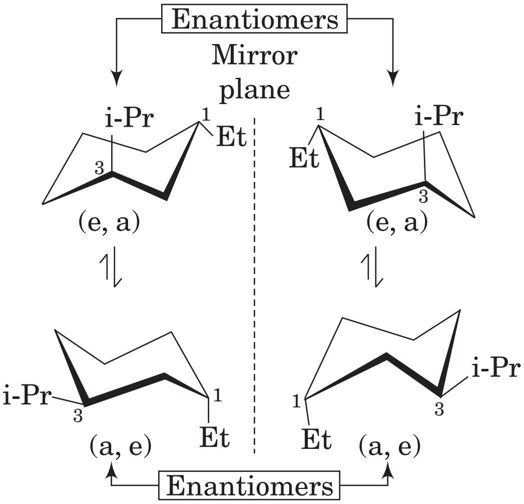


trans-1-Ethyl-2-methylcyclohexane
(resolvable)

2. 1,3-Disubstituted cyclohexane When the two substituents in a 1,3-disubstituted cyclohexane are different (e.g., 1-ethyl-3-isopropylcyclohexane), both of the *cis* and *trans* isomers are resolvable. The *cis*-isomer exists in the preferred diequatorial (e,e) conformation, while the *trans*-isomer in equatorial-axial (e, a) conformation with the bulkier substituent predominantly equatorial.

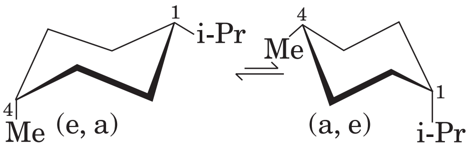


cis-1-Ethyl-3-isopropylcyclohexane
(resolvable)

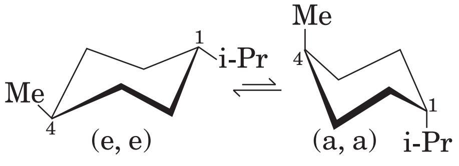


trans-1-Ethyl-3-isopropylcyclohexane
(resolvable)

3. 1, 4-Disubstituted cyclohexane Both the *cis* and *trans* isomers of a 1,4-disubstituted cyclohexane with two different substituents (e.g., 1-isopropyl-4-methylcyclohexane) are achiral due to presence of a σ plane passing through C-1 and C-4. The *trans*-isomer exists in preferred diequatorial (e,e) conformation, while the *cis*-isomer exists in equatorial-axial (e,a) conformation with the bulkier substituent predominantly equatorial.



cis-1-Isopropyl-4-methylcyclohexane
(optically inactive)

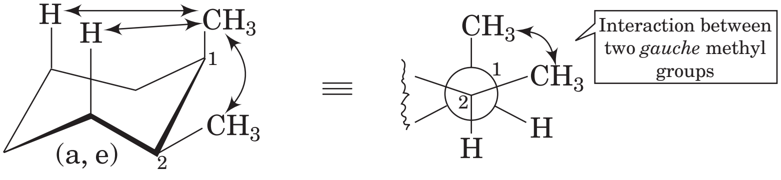


trans-1-Isopropyl-4-methylcyclohexane
(optically inactive)

3. Conformational analysis

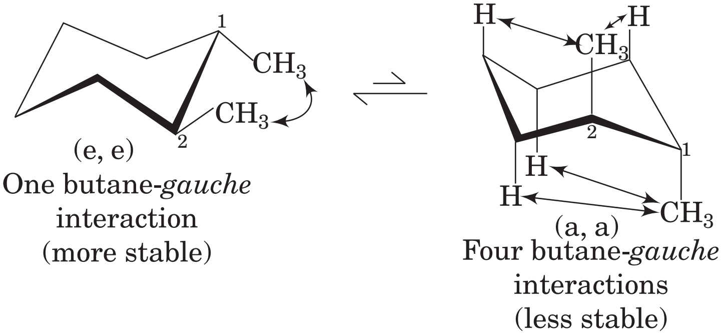
Disubstituted cyclohexanes, like monosubstituted cyclohexane, can be subjected to conformational analysis. The relative stability of the two chair conformations is determined by comparing the 1,3-diaxial interactions (or butane-*gauche* interactions) in each conformation. The relative energies of the various conformations of the *cis-trans* isomers of 1,2-, 1,3- and 1,4-dimethylcyclohexane may be determined as follows:

***cis*-1,2-Dimethylcyclohexane:** Its two chair conformations (each containing one axial and one equatorial methyl group) have the same energy. Each of them has three butane-*gauche* interactions (two originate from two Me/H 1,3-diaxial interaction and one originates from two *gauche* methyl groups) and therefore, its instability (strain energy) amounts to 3 × 0.9 = 2.7 kcal/mol (11.2 kJ/mol).



cis-1,2-Dimethylcyclohexane having three butane-*gauche* interactions

***trans*-1,2-Dimethylcyclohexane:** Its diaxial conformation has four butane-*gauche* interactions (originate from four Me/H 1,3-diaxial interactions) and its diequatorial conformation has only one butane-*gauche* interaction (originate from two *gauche* methyl groups). The diaxial conformation is destabilized by an amount of 4 × 0.9 = 3.6 kcal/mol (15.12 kJ/mol) and the diequatorial conformation is destabilized by an amount of 0.9 kcal/mol (4.2 kJ/mol). Therefore, the diequatorial conformation is more stable than the diaxial conformation by an amount of 3.6 – 0.9 = 2.7 kcal/mol and because of this, the *trans*-isomer exists almost entirely (99%) in the diequatorial (e,e) form at room temperature.



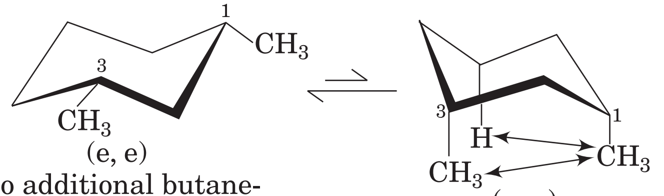
(e, e)
One butane-*gauche* interaction
(more stable)

(a, a)
Four butane-*gauche* interactions
(less stable)

trans-1, 2-Dimethylcyclohexane

trans-1, 2-Dimethylcyclohexane is more stable than its *cis*-isomer, because both methyl groups are equatorial in the more stable conformation of the former, while one methyl group must be axial in the *cis*-isomer.

***cis*-1,3-Dimethylcyclohexane:** Its diaxial conformation has two butane-*gauche* interactions and one *syn*-diaxial interaction between the two axial methyl groups. One Me/Me 1,3-diaxial interaction imparts 3.6 kcal/mol. Thus, the instability of this conformation amounts to $(2 \times 0.9 + 3.6) = 5.4$ kcal/mol (22.7 kJ/mol). The diequatorial conformation, on the other hand, has no additional interaction arising out of equatorial methyls. Therefore, it is very much stable than the diaxial form and as a consequence, the compound exists nearly exclusively in the diequatorial form.

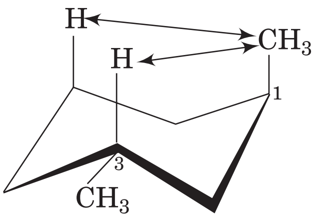


(e, e)
No additional butane-*gauche* interaction
(more stable)

(a, a)
Two butane-*gauche* and one Me/Me *syn*-diaxial interactions
(less stable)

cis-1,3-Dimethylcyclohexane

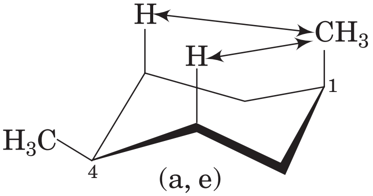
***trans*-1,3-Dimethylcyclohexane:** It has two butane-*gauche* interactions due to one axial methyl group. Its instability amounts to $2 \times 0.9 = 1.8$ kcal/mol (7.56 kJ/mol).



Two butane-*gauche* interactions
in *trans*-1,3-dimethylcyclohexane

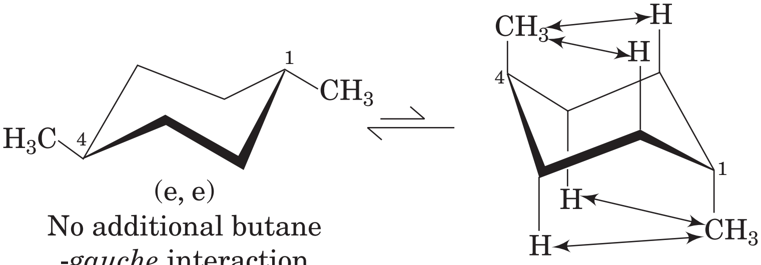
cis-1,3-Dimethylcyclohexane is more stable than *trans*-1,3-dimethylcyclohexane because both methyl groups are equatorial in the more stable conformation of the *cis*-isomer, while one methyl group must be axial in the *trans*-isomer.

***cis*-1,4-Dimethylcyclohexane:** It has two butane-*gauche* interactions due to one axial methyl group. Its interaction energy amounts to 2 × 0.9 = 1.8 kcal/mol (7.56 kJ/mol).



(a, e)
Two butane-*gauche* interactions
in *cis*-1,4-dimethylcyclohexane

***trans*-1,4-Dimethylcyclohexane:** Its diaxial conformation has four butane-*gauche* interactions. Thus, its instability amounts to 4 × 0.9 = 3.6 kcal/mol (15.1 kJ/mol). The diequatorial form, on the other hand, has no additional butane-*gauche* interaction. Hence, it is much more stable than the diaxial form and as a consequence, the compound exists almost exclusively in the diequatorial form.



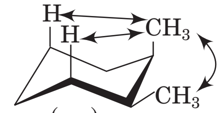
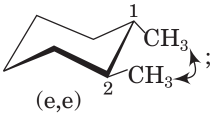
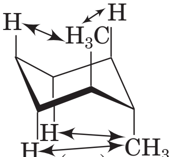
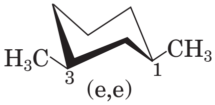
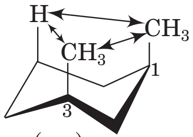
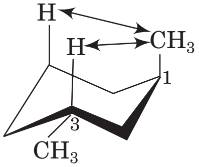
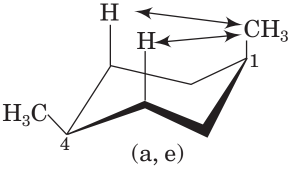
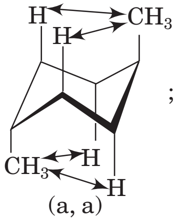
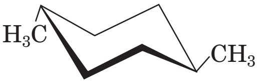
(e, e)
No additional butane
-*gauche* interaction
(more stable)

(a, a)
Four butane-*gauche* interactions
(less stable)

trans-1,4-Dimethylcyclohexane

trans-1, 4-Dimethylcyclohexane is more stable than its *cis*-isomer because both methyl groups are equatorial in the more stable conformation of the *trans*-isomer, while one methyl group must be axial in the *cis*-isomer.

Chirality and strain energy of various dimethylcyclohexanes can be seen at a glance in the following table:

Dimethyl-cyclohexane	Conformations (orientation of bond)	Optical activity	Strain energy
cis-1,2-	(e,a) $\rightleftharpoons$ (a,e) └Conformational┘ enantiomers (both up or both down)	Optically inactive (non-resolvable *dl*-pair)	 (a,e) 3 × 0.9 = 2.7 kcal/mol
trans-1,2-	(e,e) $\rightleftharpoons$ (a,a) One enantiomer (one up and one down)	Resolvable	 (e,e) 0.9 kcal/mol ;  (a,a) 4 × 0.9 = 3.6 kcal/mol
cis-1,3-	(a,a) $\rightleftharpoons$ (e,e) └Conformational┘ diastereoisomers (both up or both down)	Optically inactive (a *meso*-compound having a σ-plane)	 (e,e) No additional butane-*gauche* interaction ;  (a,a) 2 × 0.9 + 3.6 (for Me/Me) = 5.4 kcal/mol
trans-1,3-	(e, a) $\rightleftharpoons$ (a, e) One enantiomer (one up and one down)	Resolvable	 (a,e) 2 × 0.9 = 1.8 kcal/mol
cis-1,4-	(a, e) $\rightleftharpoons$ (e, a) └Identical┘ (both up or both down)	Optically inactive (σ-plane)	 (a, e) 2 × 0.9 = 1.8 kcal/mol
trans-1,4-	(e, e) $\rightleftharpoons$ (a, a) └Conformational┘ diastereoisomers (one up and one down)	Optically inactive (σ-plane and centre of symmetry)	 (a, a) 4 × 0.9 = 3.6 kcal/mol ;  (e, e) No additional butane-*gauche* interaction

SOLVED PROBLEMS

1. **Calculate the equilibrium constant (K_{eq}) at 25°C for the equilibrium: axial methylcyclohexane $\rightleftharpoons$ equatorial methylcyclohexane (the energy difference between the axial and equatorial conformations is 1.8 kcal mol^{-1}, i.e., $\Delta H = -1.8$ kcal mol^{-1}) and using that value calculate the percentage composition of the mixture.**

Solution Since ΔS for the chair-chair interconversion is very small (1 mol $\rightleftharpoons$ 1 mol), $\Delta G = \Delta H$. Hence, $\Delta G = -1.8$ kcal/mol $= -1800$ kcal/mol. ΔG is related with K_{eq} as follows:

$$\Delta G = -2.303\ \text{RT} \log K_{eq}$$

$$\therefore \quad -1800 = -2.303\ (2.00\ \text{cal/mol K})\ (298\ \text{K}) \log K_{eq}$$

Hence, $\log K_{eq} = 1.313$ and $K_{eq} = 20.6$

Now, $$K_{eq} = \frac{[\text{equatorial conformation}]}{[\text{axial conformation}]} = \frac{20.6}{1}$$

$\therefore$ % of the equatorial conformation

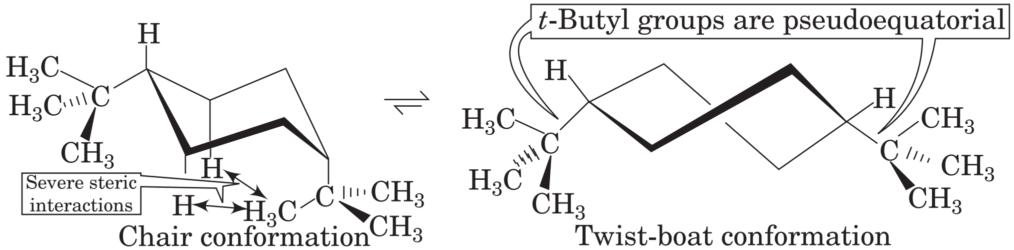
$$= \frac{[\text{equatorial conformation}]}{[\text{equatorial conformation}] + [\text{axial conformation}]} \times 100$$

$$= \frac{20.6}{(20.6 + 1)} \times 100 = 95$$

$\therefore$ % of the axial conformation = (100 – 95) = 5

2. **Predict the most stable conformation of *cis*-1,4-di-*t*-butylcyclohexane.**

Solution Either of the two chair conformations of *cis*-1,4-di-*t*-butylcyclohexane in which a bulky *tert*-butyl group occupies an axial position is very much unstable due to excessive steric interactions (1,3-diaxial interactions). To get rid of this steric strain, the molecule assumes a more stable twist-boat conformation in which the two *tert*-butyl groups are so placed that the strain is minimized.

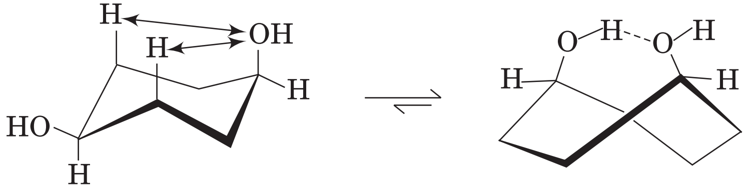


Chair conformation
(less stable)

Twist-boat conformation
(more stable and strongly preferred)

3. **Although the –OH group is not so bulky, *cis*-1,4-cyclohexanediol exists preferably in twist-boat conformation. Explain.**

Solution In the twist-boat conformation of *cis*-1,4-cyclohexanediol, the two hydroxyl groups are within hydrogen bonding distance. Because of this, this conformation is stabilized by intramolecular hydrogen bonding. In fact, it is more stable than the chair conformation (e, a) which suffers from 1, 3-diaxial interactions and for this reason, this diol exists preferably in twist-boat conformation.

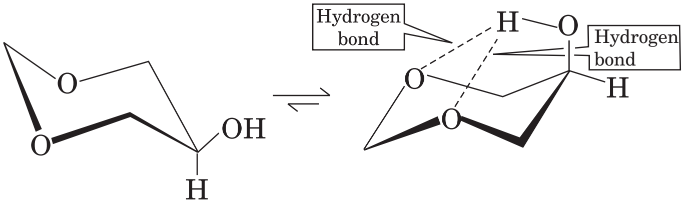


Chair conformation (less stable)

Twist-boat conformation (more stable)

4. **It is a general rule that any susbstituent is more stable in an equatorial position than in an axial one. However, 5-hydroxy-1,3-dioxane prefers to exist in axial conformation. Explain.**

Solution Due to absence of axial hydrogens at 3-positions, the axial conformation of 5-hydroxy-1,3-dioxane does not suffer from 1,3-diaxial interactions. In fact, this conformation is stabilized by intramolecular hydrogen bonding involving the ring O atoms. For this reason, this dioxane prefers to exist in the conformation with the –OH group axial.

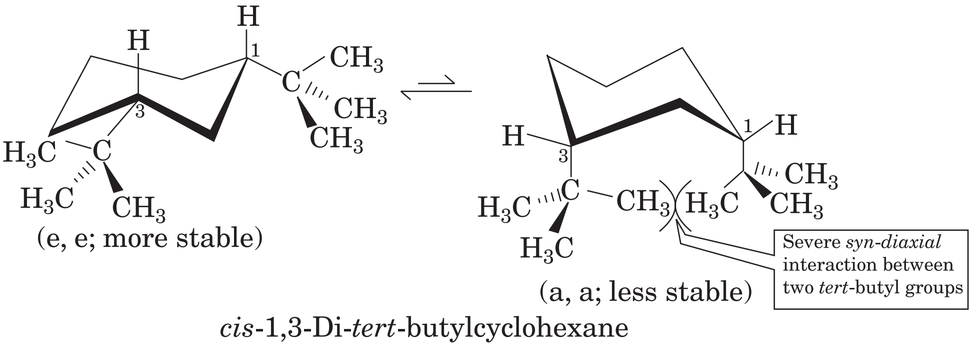


Equatorial conformation (less stable)

Axial conformation (more stable)

5. **Draw the chair conformation of *cis*-1,3- and *trans*-1,4-di-*tert*-butylcyclohexane and indicate the more stable one in each case.**

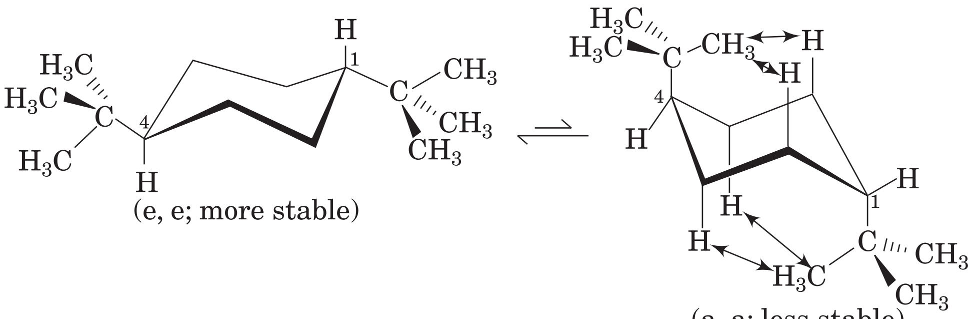
Solution The chair conformations of *cis*-1,3- and *trans*-1,4-di-*tert*-butylcyclohexane can be drawn as follows:


H
H
1
3
C
CH3
CH3
CH3
H3C
C
H3C
CH3
H
3
1
H
C
H3C
CH3
H3C
H3C
CH3
CH3
Severe syn-diaxial interaction between two tert-butyl groups

(e, e; more stable)

(a, a; less stable)

cis-1,3-Di-*tert*-butylcyclohexane



(e, e; more stable)

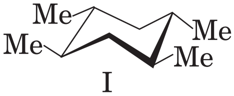
(a, a; less stable)

trans-1,4-Di-*tert*-butylcyclohexane

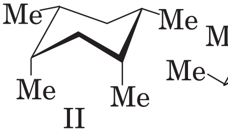
The diequatorial conformations are much more stable than the diaxial conformations which are very much destabilized by severe steric interactions involving two axial and very bulky *tert*-butyl groups.

6. **Draw the chair conformations of five diastereoisomeris forms of 1,2,4,5-tetramethylcyclohexanes and comment on their stability and chirality.**

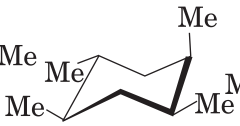
Solution The stable chair conformations of five diastereoisomeric forms of 1,2,4,5-tetramethylcyclohexanes may be drawn as follows:



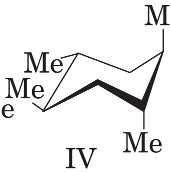
I



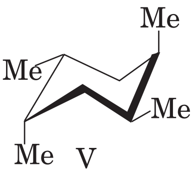
II



III

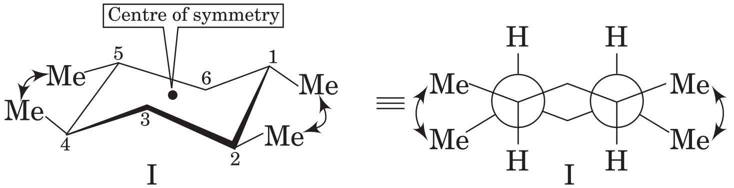


IV



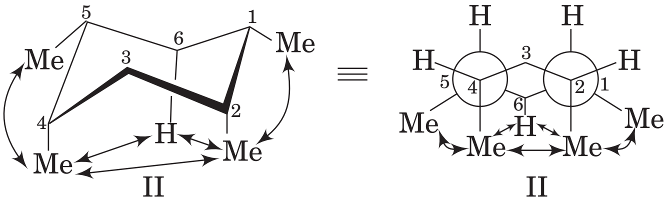
V

Configurational diastereoisomer I It has only two butane-*gauche* interactions. It is an achiral form having a plane of symmetry (σ) (passing through C-3 and C-6) along with a centre of symmetry (i). This on ring inversion produces a highly unstable chair conformation (conformational diastereoisomer).



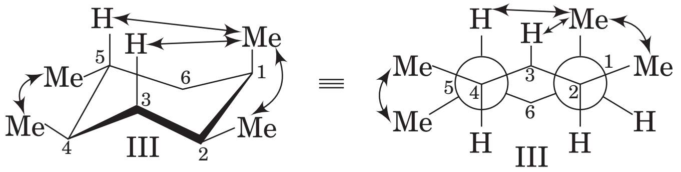
(Achiral/two butane-*gauche*)

Configurational diastereoisomer II It has four butane-*gauche* and one *syn-diaxial* interaction between two methyl groups. It is an achiral isomer having a plane of symmetry passing through C-3 and C-6. Flipping of II gives a diastereoisomeric highly unstable chair conformation.



(Achiral/four butane-*gauche* and one Me/Me)

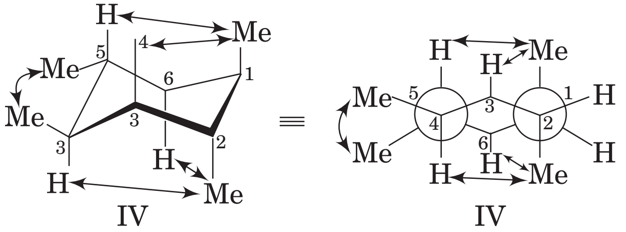
Configurational diastereoisomer III It is a chiral system and has four butane-*gauche* interactions.



(Chiral/four butane-*gauche*)

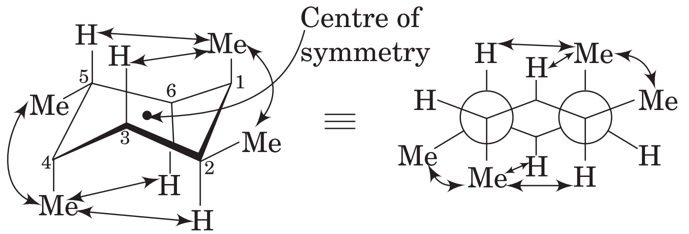
Flipping of II gives a diastereoisomeric highly unstable chair conformation.

Configurational diastereoisomer IV It is a chiral molecule and can be resolved into two enantiomers. It has five butane-*gauche* interactions. Ring inversion gives equivalent (superimposable) conformation.



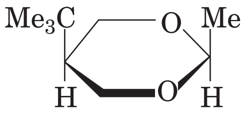
(Chiral/five butane-*gauche*)

Configurational diastereoisomer V The molecule, having a centre of symmetry, is achiral. It has six butane-*gauche* interactions. Ring inversion gives equivalent (superimposable) conformation.

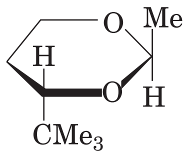


(Achircal/six butane-*gauche*)

7. **In *cis*-2-methyl-5-*tert*-butyl-1,3-dioxane (I), the conformation with *tert*-butyl axial is more favoured than the conformation with *tert*-butyl equatorial. Explain this observation. Predict the favoured conformation for *trans*-2-methyl-4-*tert*-butyl-1,3-dioxane (II).**

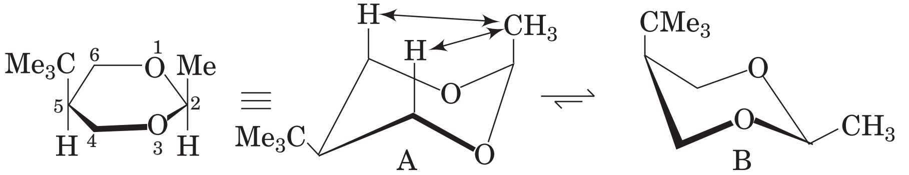


I



II

Solution The two chair conformations of *cis*-2-methyl-5-*tert*-butyl-1,3-dioxane (I) may be shown as follows:



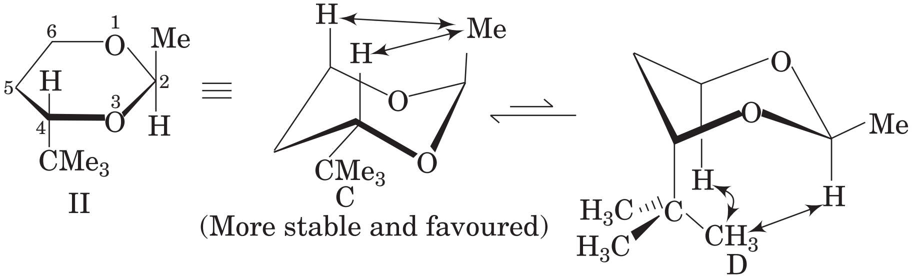
I

A
(Less stable)

B
(More stable and favoured)

The conformation A is destabilized by the *syn-axial* interactions between CH_3 and H's at C-4 and C-6. The bulky *tert*-butyl group assumes an axial position in conformation B. Nevertheless, it is free of *syn-axial* interaction because 1,3-*syn-axial* positions are now occupied by oxygen atoms having lone pair of electrons which have a smaller steric requirement than the C—H bonds. Therefore, this configuration is relatively stable and the favoured one.

The two chair conformations of *trans*-2-methyl-4-*tert*-butyl-1,3-dioxane (II) may be drawn as follows:



II

C
(More stable and favoured)

D
(Less stable)

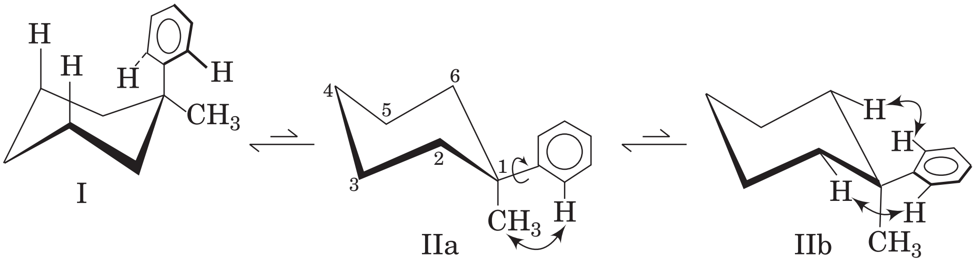
Both the chair conformations (C and D) are destabilized by *syn-axial* interactions. However, the interaction involving the larger *tert*-butyl group is much stronger than the interactions involving the smaller methyl group and because of this, the conformation C is much more stable than the conformation D and consequently, it is the favoured one.

8. **What factors make the cyclohexane ring the most stable, abundant and important ring structure in organic chemistry?**

Solution Cyclohexane would not be stable if it had a planar hexagonal ring and this is because in that shape it suffers from angle strain (bond angles of 120°, considerably larger than 109.5°) and eclipsing strain (from the six pairs of C—H bonds). Cyclohexane overcomes these strains by being puckered to give two rapidly equilibrating *chair conformations* in which it achieves nearly tetrahedral angles with no angle strain and it eliminates eclipsing strain because all C—H bonds are staggered.

9. Which one is the most stable conformation of 1-methyl-1-phenylcyclohexane and why?

Solution The possible chair conformations of 1-methyl-1-phenylcyclohexane are as given below:

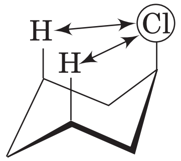


I IIa IIb

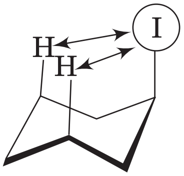
The conformational free energy of the phenyl group is 2.87 kcal/mol and that of the methyl group is 1.70 kcal/mol. Therefore, the equatorial phenyl-axial methyl conformation (IIa or IIb) is expected to be the preferred one. In fact, the conformation I with axial phenyl and equatorial methyl is the preferred one (by 0.32 kcal/mol). In conformation IIa in which the phenyl group remains in the same vertical plane passing through C-1 and C-4 of cyclohexane chair, a steric interaction develops between the axial methyl group and one of the *ortho*-hydrogen atoms of the phenyl group. Again in conformation IIa, where the phenyl group exists in nearly the same average plane (which bisects each C—C bond) of the cyclohexane chair, a severe steric strain develops between the equatorial hydrogens at C-2, C-6 and *ortho* hydrogens of the phenyl group. This type of steric interactions are absent in conformation I. The phenyl group in it is so oriented that it interacts minimally with the axial hydrogens at C-3 and C-5. Therefore, the conformation I is the more stable and preferred conformation of 1-methyl-1-phenylcyclohexane.

10. Although the size of iodine is larger than chlorine, the conformational free energy values of Cl and I atoms are almost identical. Explain this observation.

Solution Since iodine atom is larger in size than the chlorine atom, the C—I bond is longer in length compared to the C—Cl bond and this causes the I atom to remain much away from the *syn-axial* hydrogens at C-3 and C-5 compared to Cl. Thus the steric interaction which is expected to be increased on going from chlorine to iodine is compensated by simultaneous increase in distance between the *syn-axial* hydrogen atoms and the halogen atom. Because of this, the conformational free energy values of Cl (2.68 kJ mol^{-1}) and I (2.55 kJ mol^{-1}) are almost identical, even though the size of iodine (atomic radius = 1.33 Å) is larger than that of chlorine (atomic radius = 0.99 Å).



Chlorocyclohexane



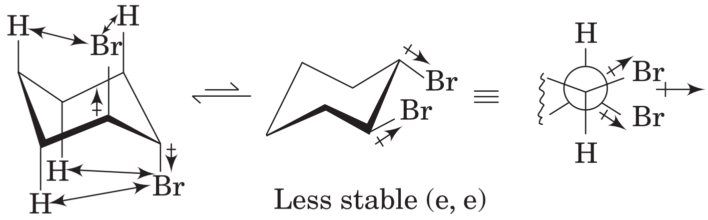
Iodocyclohexane

[The difference in free energy between an equatorial and an axial conformation is known as the conformational free energy ($-\Delta G°_R$ or A-value) of the substituent (R) and determines the equatorial preference of R.]

11. In gaseous state, the diaxial conformation of *trans*-1,2-dibromocyclohexane is much more stable than the diequatorial conformation (a,a : e,e = 95 : 5). However, in benzene both the conformations are nearly equally stable (a,a : e,e = 52 : 48). Explain these observations.

Solution In the diaxial conformation of *trans*-1,2-dibromocyclohexane, the two dipoles are oppositely placed ($\theta = 180°$). So, its dipole moment is nearly zero and there is no electrostatic repulsion between them. However, it is slightly destabilized by 1,3-diaxial interactions. In the diequatorial conformation, on the other hand, the two dipoles are oriented at a dihedral angle of 60°. So, there is considerable electrostatic repulsion and because of this, it is much destabilized compared to the diaxial conformation. In the gaseous state, the molecules remain much separated from each other, and so, there operates no intermolecular forces (dipole-dipole interaction) which may stabilize the diequatorial form. As a result, the more stable diaxial conformation exists predominantly (95 : 5). However, in benzene solution, the molecules come much closer to each other and as a consequence, the electrostatic repulsion between the two dipoles in the diequatorial form is minimized due to intermolecular dipole-dipole attraction. Because of this, the two conformations become nearly equally stable and remain almost equally populated (52 : 48).

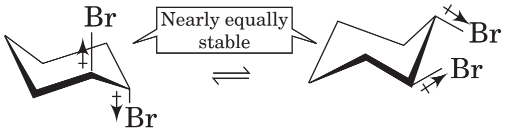
***trans*-1,2-Dibromocyclohexane:**
In gaseous state:



More stable (a, a) conformation (95%)

Less stable (e, e) conformation (5%)

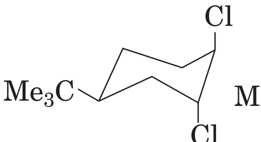
In benzene solution:



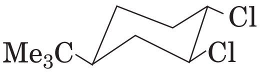
(a, a) conformation (52%)

(e, e) conformation (48%)

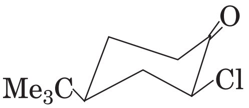
12. How can the dipole moment (μ) values be used to distinguish between: (i) the diastereoisomeric 1,2-dichloro-4-*tert*-butylcyclohexanes (A and B) and (ii) the diastereoisomeric 2-chloro-4-*tert*-butylcyclohexanones (C and D)?



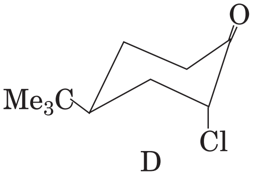
A



B



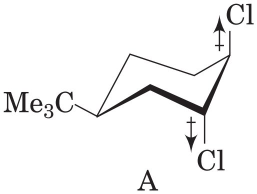
C



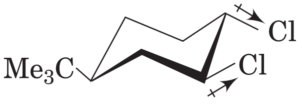
D

Solution

(i) Due to presence of the very bulky equatorial —CMe$_3$ group at C-4, A and B are anancomeric (flipping restricted) system. In A, the two C—Cl bond moments nearly cancel each other. Consequently, its resultant dipole moment value will be less than that of B in which the two C–Cl bond moments are separated by a dihedral angle of 60°. Therefore, the μ value of the isomer B will be higher than that of the isomer A and thus, they can be easily distinguished by their dipole moment values.



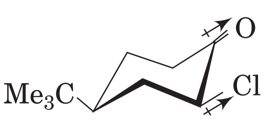
A
(less polar)



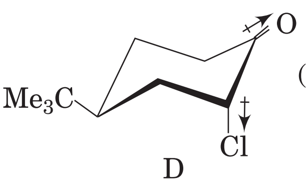
B
(more polar)

($\mu_B > \mu_A$)

(ii) Due to the same basic reason, C and D are also anancomeric systems. Unlike the isomer D, the C=O and C—Cl bond moments in C operate approximately in the same direction. Consequently, C must have higher dipole moment than D and thus, they can be easily distinguished by measuring their dipole moment values.



C
(more polar)

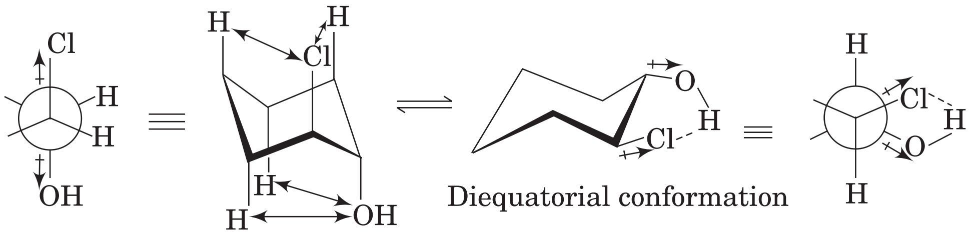


D
(less polar)

($\mu_C > \mu_D$)

13. The two chair conformations of *trans*-2-chlorocyclohexanol are equally populated—Comment on this observation.

Solution The diequatorial conformation of *trans*-2-chlorocyclohexanol is stabilized by intramolecular hydrogen bonding, but destabilized by the electrostatic repulsion between the two dipoles. On the other hand, the diaxial conformation is somewhat destabilized by 1,3-diaxial interaction, even though it has the advantage of the absence of electrostatic repulsion between the two dipoles. A compromise is reached and the two conformations are found to be almost equally populated.



Diequatorial conformation

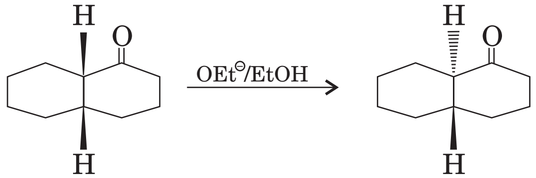
Diaxial conformation

trans-2-Chlorocyclohexanol

14. Explain the following observations:

(a) *cis*-5-*tert*-Butyl-2-methylcyclohexanone undergoes isomerization to yield the *trans*-isomer in the presence of a base.

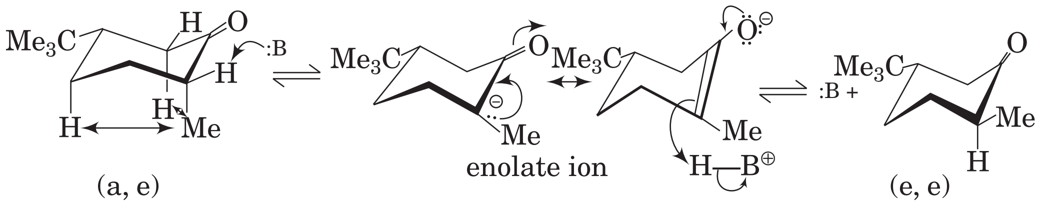
(b)



cis-2-Decalone *trans*-2-Decalone

Solution

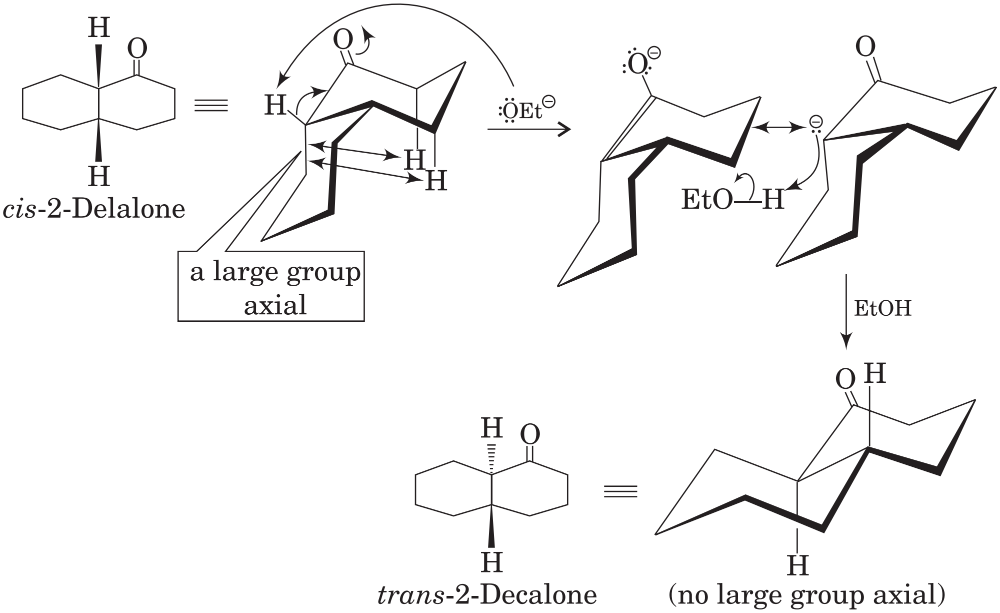
(a) In the *cis*-isomer of 5-*tert*-butyl-2-methylcyclohexanone, the bulky —CMe_3 group (the anchoring group) holds the —CH_3 group axial and as a consequence, it suffers from 1,3-diaxial interactions. In the *trans*-isomer, on the other hand, the equatorial —CH_3 group is too far to experience any appreciable steric interaction with C=O and also eclipsing of —CH_3 and C=O is electronically favourable. Therefore, the *trans*-isomer is relatively more stable than the *cis*-isomer and because of this, when treated with a base, the *cis*-isomer is isomerized to the *trans*-isomer through the formation of an intermediate enolate ion.



(a, e)
cis-5-*tert*-Butyl-2-methylcyclohexanone
(less stable)

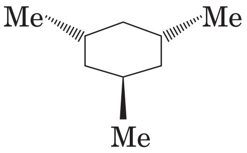
(e, e)
trans-5-*tert*-Butyl-5-methylcyclohexanone
(more stable)

(b) In *cis*-2-decalone, a large group is axial. So, because of 1,3-diaxial interactions, it is thermodynamically less stable than *trans*-decalone in which no large group is axial. For this reason, when *cis*-2-decalone is treated with a base, it becomes converted to the more stable *trans*-2-decalone through the formation of an intermediate enolate ion.

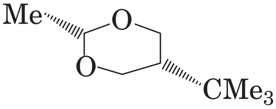


15. Draw the more and less stable conformations for each of the following compounds:

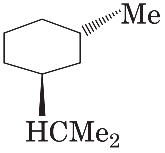
(a)



(b)

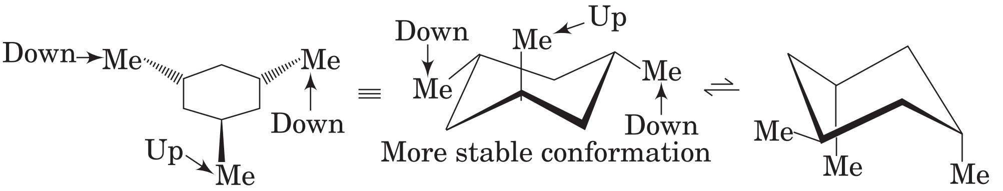


(c)



Solution

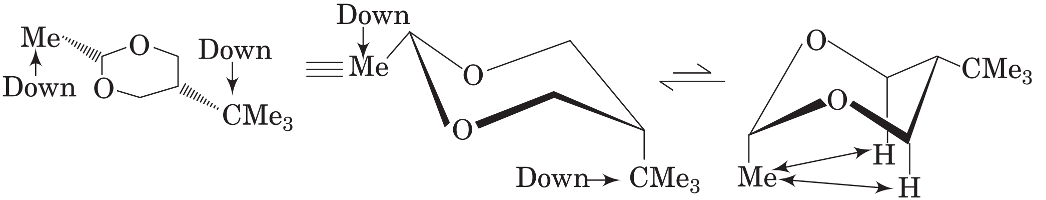
(a) The more stable conformation is that in which maximum number of substituents are equatorially placed.



More stable conformation

Less stable conformation

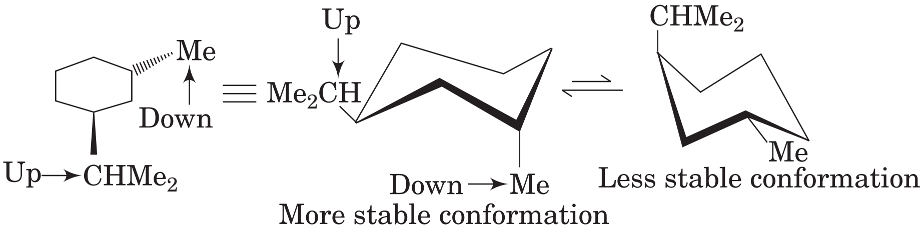
(b) The more stable conformation is that which places the bulkier *tert*-butyl group axial and that is because it does not suffer from 1,3-diaxial interactions.



More stable conformation

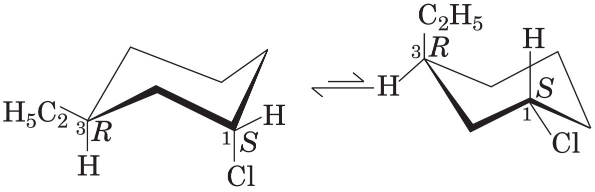
Less stable conformation

(c) The more stable conformation is that which places the bulkier isopropyl group equatorial.



16. Draw the chair conformations of (1*S*, 3*R*)-3-ethyl-1-chlorocyclohexane. Predict whether it is a *cis* or *trans*-isomer.

Solution The two chair conformations of (1*S*, 3*R*)-3-ethyl-1-chlorocyclohexane are as follows:

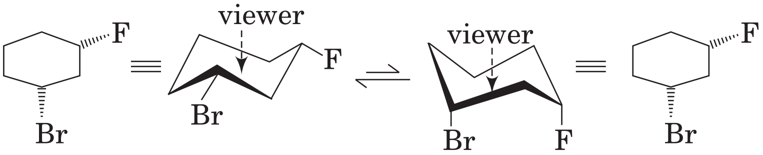


[The absolute configurations of the asymmetric carbons remain unchanged on ring inversion.]

In this disubstituted cyclohexane one bond is pointing upward and the other downward. Therefore, it is the *trans*-isomer.

17. A planar structure does not convey any conformational information. Explain with an example.

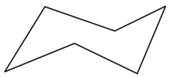
Solution So long as all conformations are viewed from the same face of the ring, flipping does not interchange wedges and dashed lines because it does not change the up or down relationship of the ring substituents. For example, both the conformations of 1-bromo-3-fluorocyclohexane can be represented by single planar structure.



Thus, a planar structure does not convey any conformational information.

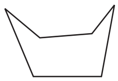
18. Give an example of pseudorotation.

Solution The term pseudorotation is used to describe a variety of conformational changes in cyclic systems which are low-energy processes and do not involve bond angle variations but only changes in torsional strain and other non-bonded interactions, as in the transformations of the flexible forms of cyclohexanes (but not the chair-chair interconversion) such as follows:



Chair form
of cyclohexane

$\rightleftharpoons$

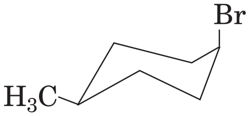


Boat form
of cyclohexane

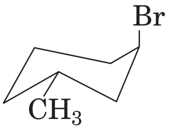
STUDY PROBLEMS

1. Predict the more stable conformation of *trans*-1,3-di-*tert*-butylcyclohexane.
2. Determine whether each of the following compounds is a *cis*-isomer or a *trans*-isomer.

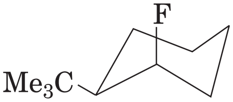
(a)



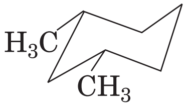
(b)



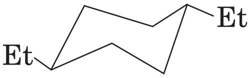
(c)



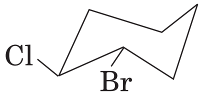
(d)



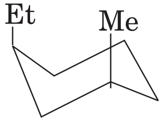
(e)



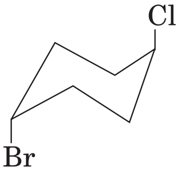
(f)



(g)

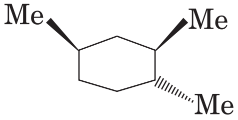


(h)

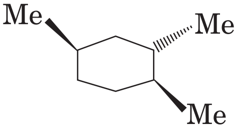


3. Identify the more stable stereoisomer in each of the following pairs and give your reasoning:

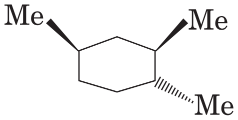
(a)



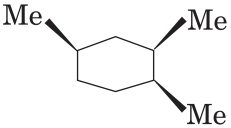
or



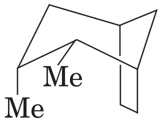
(b)



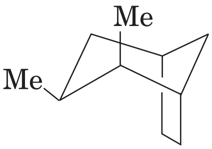
or



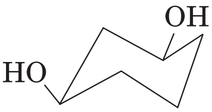
(c)



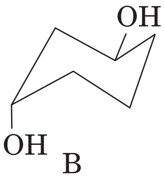
or



4. The dipole moment of *trans*-1, 3-dibromocyclobutane is 1.1 D. Explain why a nonzero dipole moment suggests a puckered structure rather than a planar structure for this compound.
5. Explain the observation that A forms intramolecular hydrogen bond, while B forms only intermolecular hydrogen bond.

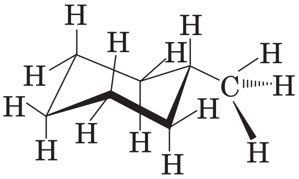


A



B

6. Even though the methyl group occupies an equatorial position, the conformation shown is not the most stable one for methylcyclohexane. Explain.



7. Identify the more stable stereoisomer in each of the following pairs, and give the reason for your choice.

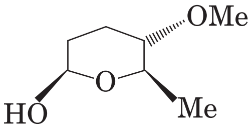
(a) *cis*- or *trans*-1-Isopropyl-2-methylcyclohexane

(b) *cis*- or *trans*-1-Isopropyl-3-methylcyclohexane

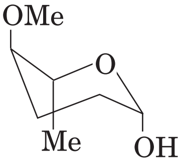
(c) *cis*- or *trans*-1-Isopropyl-4-methylcyclohexane

8. One stereoisomer of 1, 1, 3, 5-tetramethylcyclohexane is 15 kJ mol^{-1} (3.7 kcal mol^{-1}) less stable than the other. Which isomer is less stable and why?

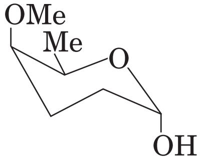
9. Which is the most stable pyranose conformation of the following carbohydrate (a component of a drug used in veterinary medicine)?



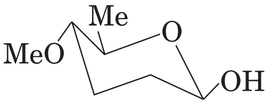
(a)



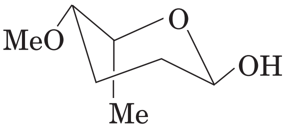
(b)



(c)



(d)



10. *cis*-1, 2-Dibromocyclohexane represents a chiral molecule but it cannot be resolved. How can you explain this observation?

11. (1*R*, 2*S*)-1,2-Dimethylcyclohexane on ring inversion remains (1*R*, 2*S*)-1, 2-dimethylcyclohexane, yet one is the mirror image of the other. Explain with chair conformation.

12. What is the most stable conformation of *trans*-1,3-di-*tert*-butylcyclohexane? Give reasons in favour of your answer.

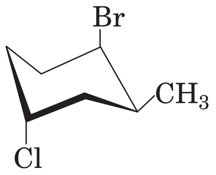
13. What product is expected to be obtained when 1,2-dimethylcyclohexene is subjected to catalytic hydrogenation (H_2/Pb)? Is the compound chiral and resolvable?

14. What do you mean by inversion of chair conformation of cyclohexane? What are the two pathways through which such an inversion is possible?

15. In 66% aqueous DMF, the *trans*-isomer of 4-*tert*-butylcyclohexanecarboxylic acid is found to be more acidic than its *cis*-isomer. Explain this observation.

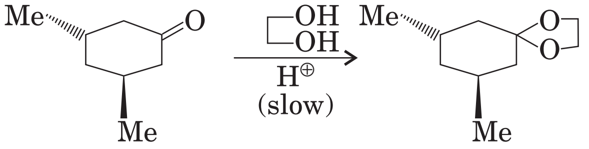
16. Suggest a reason why the energy difference between conformations of ethylcyclohexane is about the same as that for methylcyclohexane, even though the ethyl group is larger than a methyl group.

17. For the following molecule, draw its enantiomer as well as one of its diastereoisomer. Designate the (*R*) and (*S*) configuration at each chiral centre.

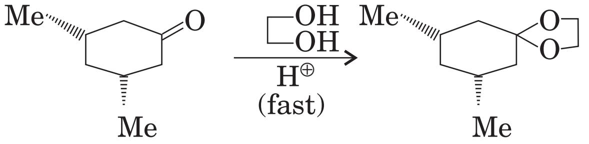


18. Explain the following observations:

(a) It is more difficult to prepare an acetal of the Compound I than the Compound II.

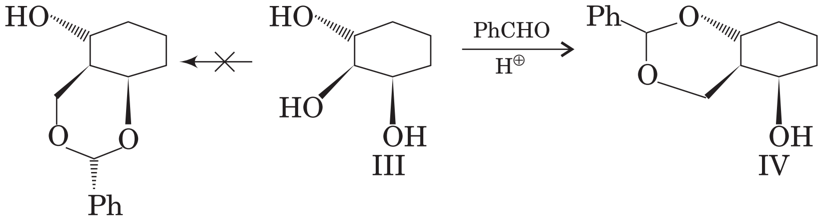


I



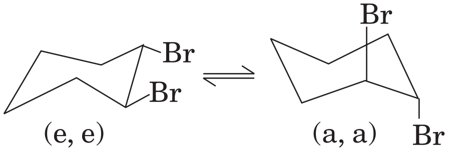
II

(b) The Compound III forms the acetal IV but not V.



V III IV

19.



Which of these two conformations is more stable in methanol (CH_3OH) and in *n*-octane? Explain.

[**Hint:** In nonpolar solvent *n*-octane, the diequatorial form, although favoured sterically is destabilized by dipole repulsion ($\mathrm{C}\!\overset{+\!\!\rightarrow}{-}\!\mathrm{Br}$ dipoles are *gauche* to each other). Consequently, the diaxial form is more stable. On the other hand, in polar solvent methanol (dielectric constant is much higher), the dipole repulsion in the diequatorial form is minimized by the intermolecular dipole-dipole attraction. Therefore, the sterically favoured diequatorial conformation is more stable in methanol.]

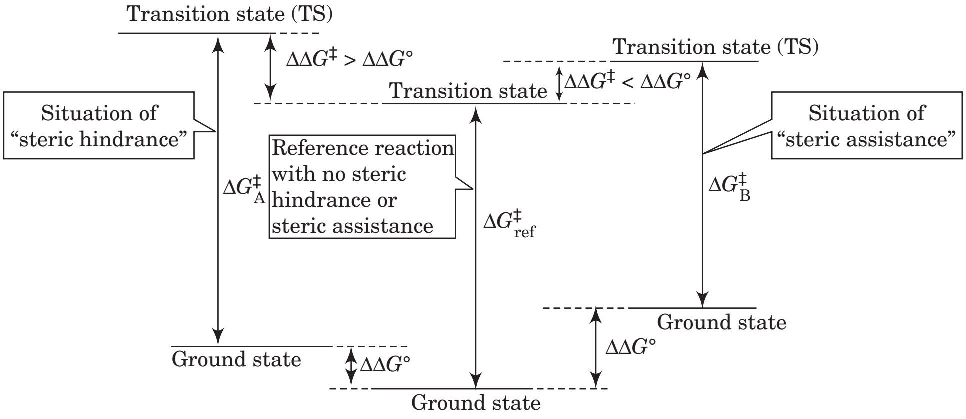
7.2 CONFORMATION AND REACTIVITY IN CYCLOHEXANES

Pioneering investigations concerning the effect of conformation on chemical reactivity have been carried out by Barton (1950). It is convenient to divide these effects into two kinds: (a) Steric effect and (b) Stereoelectronic effect.

7.2.1 Steric Effect

By steric effects we mean effects due to close approach of two groups in a molecule or between molecules such that appreciable van der Waals repulsive forces are called into play. Such effects may occur in the ground state of a molecule, or in the transition state for a given reaction, or both. van der Waals repulsive interactions can become quite large if the non-bonded distances are sufficiently short. However, it must be remembered that the van der Waals interactions can also be attractive but its effects are quite small and depend largely on the separating distance between the interactive groups. For the sake of simplicity, we shall, in the following discussion, assume that the effects are repulsive.

Two kinds of situations may arise. Steric effects can accelerate or decelerate reaction rates. When the reaction rate is slowed down due to steric effects, then it is called *steric hindrance*. This situation is very familiar in many reactions including the reactions in cyclohexanes. In the case of steric hindrance, repulsion is substantial in the transition state and small or absent in the ground state. Compared to a reference case, the activation energy in this situation is increased because the energy level of the transition state is more raised than that of the ground state. As a result, the reaction rate is slowed down. In some other cases, the steric repulsion is more important in the ground state than in the transition state and for this, the energy level of the ground state is elevated more than that of the transition state. Thus, the activation energy for the reaction is decreased and the rate of the reaction is accelerated relative to the reference case. When, the rate of a reaction is increased due to steric effects, than it is called *steric assistance*. Steric effects are very much pronounced in S_N2 displacement reactions and E2 elimination reactions. The situations of steric hindrance and steric assistance can be depicted in Fig. 7.1.


Transition state (TS)
$\Delta\Delta G^{\ddagger} > \Delta\Delta G^{\circ}$
Transition state (TS)
Transition state
$\Delta\Delta G^{\ddagger} < \Delta\Delta G^{\circ}$
Situation of "steric hindrance"
Situation of "steric assistance"
Reference reaction with no steric hindrance or steric assistance
$\Delta G^{\ddagger}_{A}$
$\Delta G^{\ddagger}_{ref}$
$\Delta G^{\ddagger}_{B}$
Ground state
Ground state
$\Delta\Delta G^{\circ}$
$\Delta\Delta G^{\circ}$
Ground state

(a) In the situation of "steric hindrance" : $\Delta G^{\ddagger}_{A} > \Delta G^{\ddagger}_{ref}$

(b) In the situation of "steric assistance" : $\Delta G^{\ddagger}_{B} < \Delta G^{\ddagger}_{ref}$

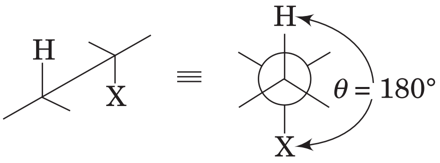
Fig. 7.1 Steric hindrance and steric assistance

7.2.2 Stereoelectronic Effect

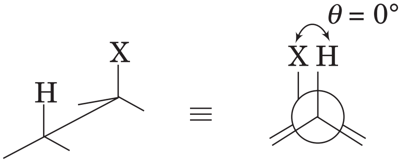
According to Deslongchamps, stereoelectronic effect is an effect on reactivity caused by the spatial disposition of specific electron pair (bonded or nonbonded) within a reactant molecule. In many cases, these are electron pairs in bonds that are formed, broken, or otherwise displaced in the reaction under investigation. In some other cases, these are unshared pair of electrons in the valence shell of exocyclic or endocyclic heteroatoms. Stereoelectronic effects are very much pronounced in S_N2 and E2 reactions. By applying the concept of stereoelectronic effects, it becomes possible to acquire knowledge of the transition states of many organic reactions.

Cyclohexane is a unique compound in the sense that in spite of having a cyclic structure, it can assume a very stable chair conformation in substituted cyclohexane under a variety of reactions. Stereoelectronic effects on reactivity in various reactions of cyclohexanes have been discussed in this chapter.

E2 reaction The stereoelectronic requirement of an E2 process is that the groups to be eliminated should be *antiperiplanar* (i.e, conformationally *trans* to one another with a dihedral angle of 180°) and not *syn-periplanar* (i.e., conformationally *cis* to one another with a dihedral angle of 0°).



Anti-periplanar conformation
(more favourable for E2)



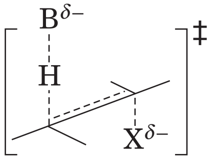
Syn-periplanar conformation
(less favourable for E2)

The stereoelectronic requirement of *anti*-periplanarity exists because of the following reasons:

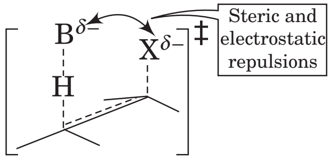
(i) Electrons from the sigma bond at the β-carbon will delocalize into the vacant orbital forming at the α-carbon atom to produce the alkene π bond. Since the p orbitals of a π bond are coplanar, it is reasonable to assume that **coplanarity** of the sigma orbitals leading to the formation of π bond will be energetically preferred.

(ii) Unlike in the *syn* geometry the attacking base and the leaving group remain far apart from each other in *anti*-geometry and therefore, the steric interactions and electrostatic repulsions are minimized.

(iii) Unlike the *syn* geometry the *anti*-geometry allows the bonding electrons from the beta substituent to displace the leaving group from the backside. This familiar backside attack is energetically advantageous from electronic point of view.

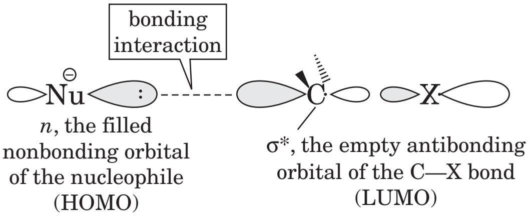


Anti-periplanar E2
transition state
(more stable)

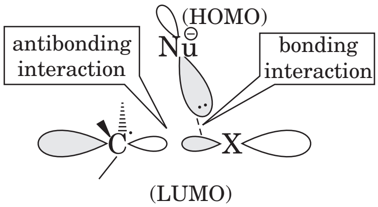


Syn-periplanar E2
transition state
(less stable)

S_N2 reaction It has long been known that an S_N2 reaction proceeds with inversion of configuration, that is, that the incoming nucleophile enters from the back of the leaving group. The stereoelectronic situation is that the σ^* orbital of the bond joining the reacting carbon and the leaving group is the one that gives rise to the new σ bond to the incoming nucleophile. The overlap is bonding when the nucleophile approaches the electrophile from the rear leading to inversion of configuration (a), but the approach from the front leading to retention of configuration (b), is both bonding and antibonding. Therefore, the former approach is clearly preferred.


bonding interaction
$\ominus$
Nu
C
X
n, the filled nonbonding orbital of the nucleophile (HOMO)
σ*, the empty antibonding orbital of the C—X bond (LUMO)

(a) Inversion of configuration
(favourable)



(b) Retention of configuration
(not favourable)

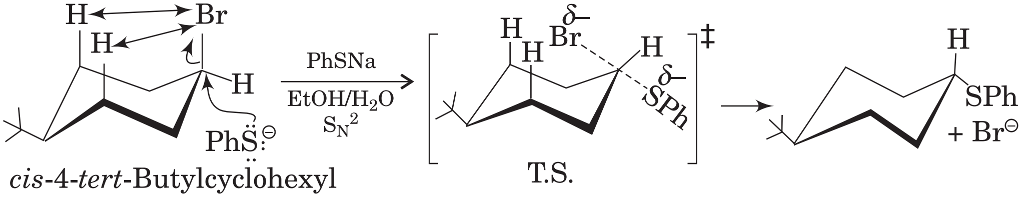
7.2.3 Reactions of Cyclohexane Derivatives

7.2.3.1 Nucleophile Aliphatic Substitutions

S_N2 reaction The rate determining step (the only step here) of bimolecular nucleophilic susbtitution reactions (S_N2) involves synchronous attack of the nucleophile and the departure of the leaving group. A stereoelectronic requirement is that the transition state has linear arrangement of the partially bonded nucleophile, the carbon atom undergoing substitution, and the partially bonded leaving group. In case of cyclohexanes, the axial conformation (leaving group) reacts more rapidly than the equatorial conformation and this is because of the following two reasons:

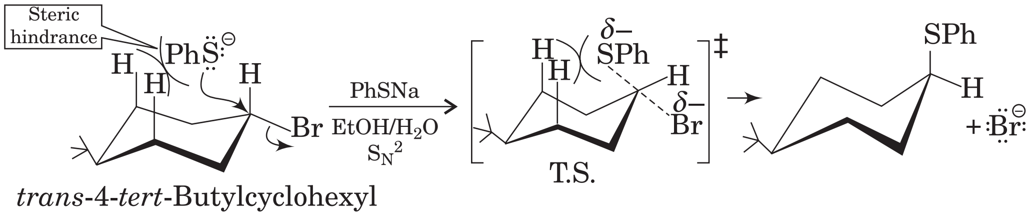
1. The axial approach of the nucleophile for an equatorial leaving group is sterically more hindered due to *syn*-axial hydrogens at C-3 and C-5 position, relative to the carbon (C-1) undergoing substitution.
2. The ground state energy of the axial isomer is higher than the equatorial isomer, and therefore, the activation energy to reach the transition state will be less for the axial isomer.

It is to be noted that these factors are important when the size of the nucleophile is larger than that of the leaving group. For example, the S_N2 reaction of *cis*-4-*tert*-butylcyclohexyl bromide with sodium thiophenoxide ($PhS^{\ominus}Na^{\oplus}$) at 25°C in aqueous ethanol occurs at a much faster rate (60 times) than the *trans*-isomer. This finding would appear to be due to a combination of steric and stereoelectronic effects. The bulky *tert*-butyl group practically locks the *cis*-isomer in that particular conformation which places bromine in the axial position. There is ground-state compression in the axial compound (*syn-axial* interactions), giving rise to an increase in ground-state energy and decrease in activation energy (steric assistance). Also, the approach of $PhS^{\ominus}$ is easier because there is large space between the axial and equatorial H atoms. For these reasons, the *cis*-isomer reacts with the bulky nucleophile thiophenoxide ion ($PhS^{\ominus}$) by S_N2 mechanism at a much faster rate.



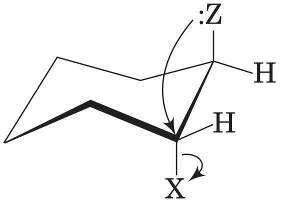
cis-4-*tert*-Butylcyclohexyl bromide

On the other hand, the *tert*-butyl group practically locks the *trans*-isomer in that particular conformation which places bromine in the equatorial position. So, unlike the *cis*-isomer, steric assistance is not available in this case. However, there is steric hindrance to backside attack (from the axial side), that is, the stereoelctronic requirement of backside attack produces an adverse steric factor in this case. For these reasons, displacement of bromine by $PhS^{\ominus}$ a much slower rate.



trans-4-*tert*-Butylcyclohexyl bromide

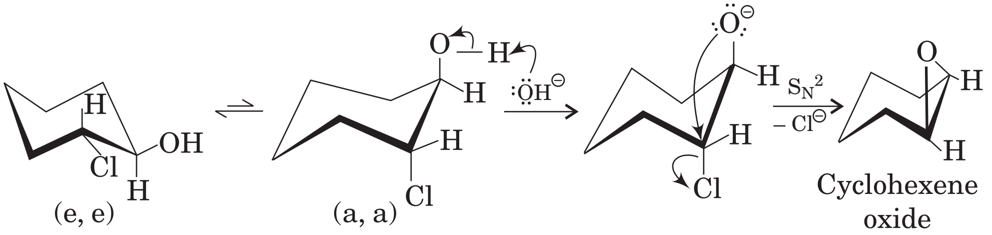
Neighbouring group participation (NGP) For neighbouring group participation to be operative in a 1,2-disubstituted cyclohexane, a *trans* diaxial arrangement of the departing and participating groups is necessary and this is because stereoelectronic requirement for S_N2 attack is fulfilled in such a conformation.



trans diaxial conformation
(good geometry for anchimeric assistance)

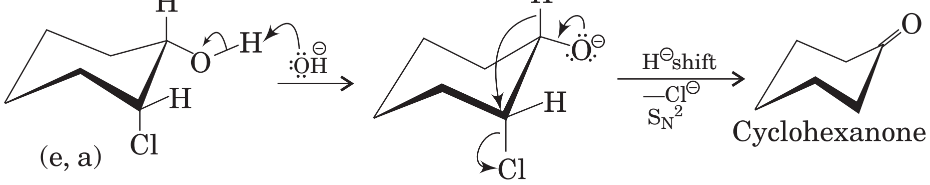
The following observations can be well explained in terms of neighbouring group participation:

1. *cis*- and *trans*-2-Chlorocyclohexanol behave differently towards alkali. The *trans*-isomer, which can attain a diaxial geometry necessary for backside attack, undergoes intramolecular S_N2 attack (displacement of chloride ion by the oxyanion) to give cyclohexene oxide.



trans-2-Chlorocyclohexanol

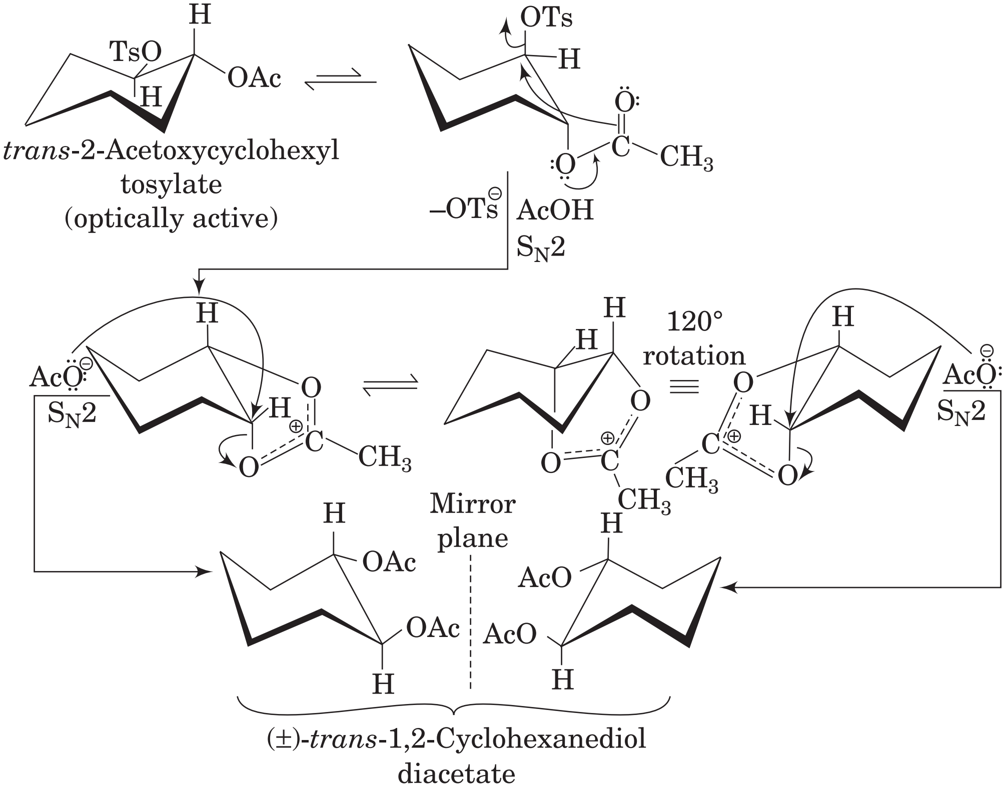
The *cis*-isomer, on the other hand, cannot attain the geometry necessary for backside attack. In this case, a slower reaction involving migration of a hydride ion occurs to form cyclohexanone.



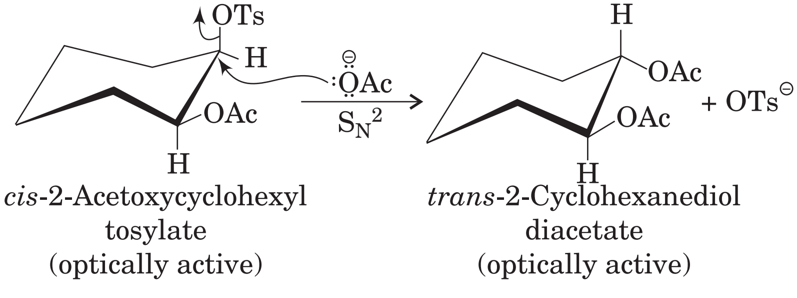
cis-2-Chlorocyclohexanol

2. **When active *trans*-2-acetoxycycohexyl tosylate is treated with KOAc in AcOH, (±)-*trans*-1,2-cyclohexanediol diacetate is obtained through a faster reaction. However, when the *cis*-isomer is treated similarly, active *trans*-1, 2-cyclohexanediol diacetate is obtained through a much slower reaction**. An acetoxy group can function as a neighbouring group. In the diaxial form of the *trans*-

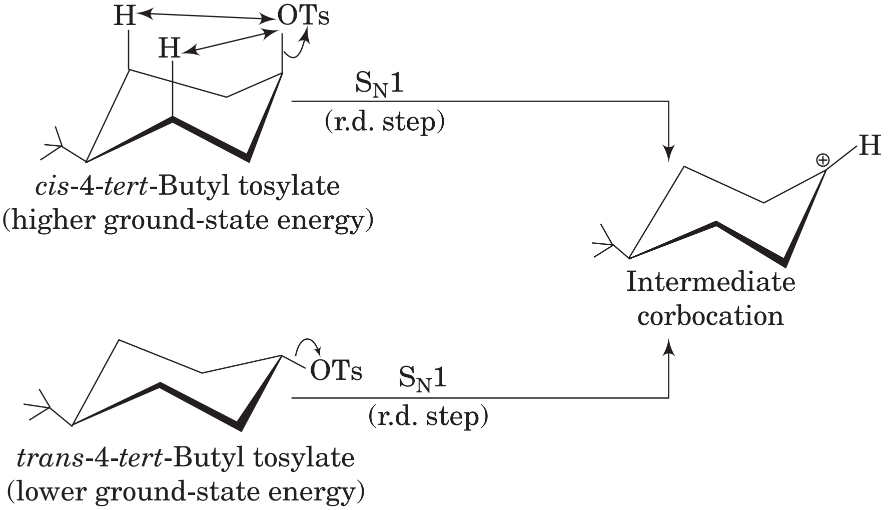
isomer, the acetoxy group is suitably placed for backside attack and so, it pushes out the tosylate anion to form an acetoxonium ion (first step) with inversion of configuration at the carbon under attack. The acetoxonium ion undergoes a ring flip to produce its mirror image. The two enantiomeric intermediates then undergo nucleophilic attack by the acetate ion (second step) again with inversion of configuration at the carbon under attack and as a result, racemic *trans*-1,2-cyclohexanediol diacetate is obtained.



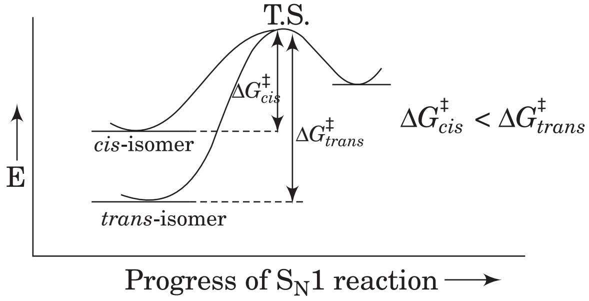
The *cis*-tosylate, on the other hand, cannot assume the diaxial conformation needed for backside attack by the acetoxy group and there is no neighbouring group effect. Thus, this isomer reacts by the normal S_N2 process to yield active *trans*-1,2-cyclohexanediol diacetate and the reaction is much slower than for the *trans*-tosylate to which the anchimeric assistance is available.


OTs
H
OAc
H
:ÖAc⊖
SN2
H
OAc
OAc
H
+ OTs⊖
cis-2-Acetoxycyclohexyl tosylate (optically active)
trans-2-Cyclohexanediol diacetate (optically active)

S_N1 reaction *cis*-4-*tert*-Butyl tosylate undergoes solvolysis in 80% ethanol at a faster rate than its *trans*-isomer. This difference in reaction rate can be well explained in terms of steric assistance. Owing to steric interaction between the axial-OTs group and the axial hydrogen atoms at C-3 and C-5, the *cis*-isomer has a higher ground state energy than the *trans*-isomer. Solvolysis (S_N1) of both of them involves a common carbocation intermediate. So, as first approximation, the T.S. of the r.d. step may also be assumed to be common for both of these reactions. Accordingly, the T.S. energy ($\Delta G^{\ddagger}$) for the *cis*-isomer will be less than the *trans*-isomer and the former will react at a faster rate.

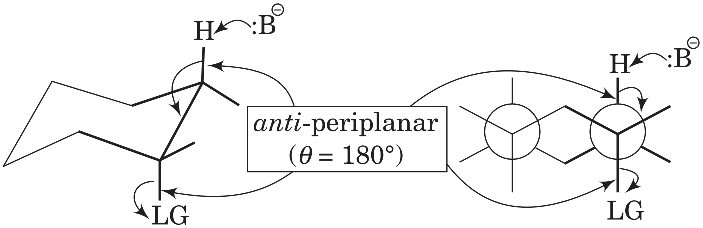

H
OTs
H
S_N1
(r.d. step)
cis-4-*tert*-Butyl tosylate
(higher ground-state energy)
⊕
H
Intermediate
corbocation
OTs
S_N1
(r.d. step)
trans-4-*tert*-Butyl tosylate
(lower ground-state energy)

This situation of 'steric assistance' can be well illustrated by the following energy diagram:



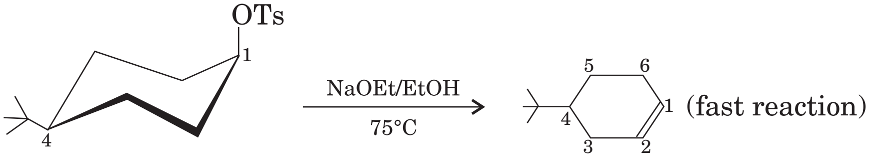
7.2.3.2 *Elimination Reactions*

(a) E2 reaction In cyclohexane derivatives, the stereoelectronic requirement of E2 reaction, i.e, the *anti*-periplanar orientation of the departing groups is satisfied only when the groups are in diaxial (a, a) positions but not in diequatorial (e, e) or equatorial-axial (e, a) positions. In fact, when they are equatorial-axial, they are *syn* to each other and also not coplanar. When they are diequatorial they are *anti* to each other but not coplanar. *They are anti as well as coplanar only when they are diaxial*. Therefore, the diaxial conformation of cyclohexane derivatives is very susceptible to E2 reaction as the stereoelectronic requirements is then fulfilled.

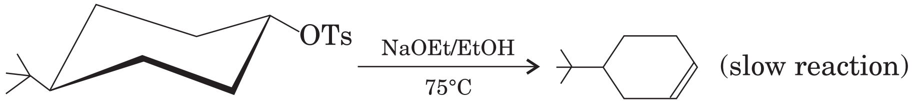


Diaxial conformation
(suitable for E2 because the stereo-electronic requirement of *anti*-periplanarity is satisfied)

When the *cis*-isomer of 4-*tert*-butylcyclohexyl tosylate is heated with NaOEt in EtOH at 75°C, it undergoes a facile E2 reaction to yield 4-*tert*-butylcyclohexene. However, the *trans*-isomer reacts slowly with NaOEt to give the same product when treated similarly.

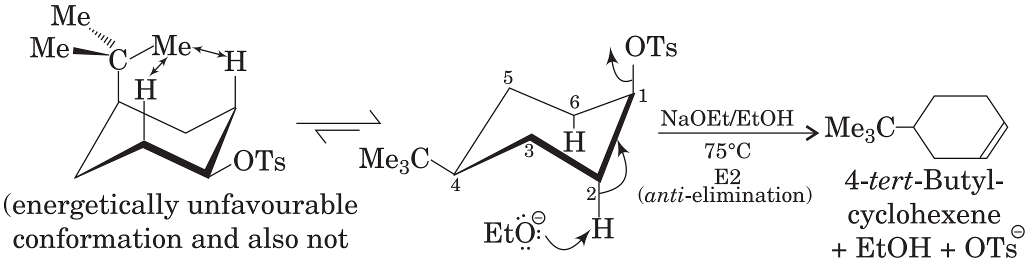


cis-4-*tert*-Butylcyclohexyl tosylate 4-*tert*-Butylcyclohexene



trans-4-*tert*-Butylcyclohexyl tosylate 4-*tert*-Butylcyclohexene

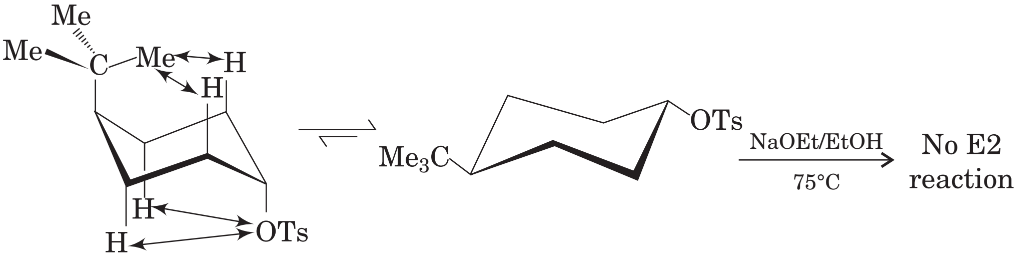
The bulky *tert*-butyl group (—<) in both *cis*- and *trans*-tosylates nearly always assumes an equatorial position, holding the ring in a single conformation predominantly. The *cis*-isomer exists nearly exclusively in the axial-tosylate conformation, while the *trans*-isomer exists nearly exclusively in the equatorial tosylate conformation. In the thermodynamically stable axial-tosylate conformation of the *cis*-isomer, the –OTs group and a *β*-H atom (either at C-2 or at C-6) are *anti*-periplanar. Because of such arrangement of the departing groups in which the stereoelectronic requirement is fulfilled, the isomer undergoes a facile E2 reaction, i.e., the loss of TsOH occurs at a faster rate.



(energetically unfavourable conformation and also not suitable for E2)

(energetically favourable conformation and also suitable for E2)
cis-4-*tert*-Butylcyclohexyl tosylate

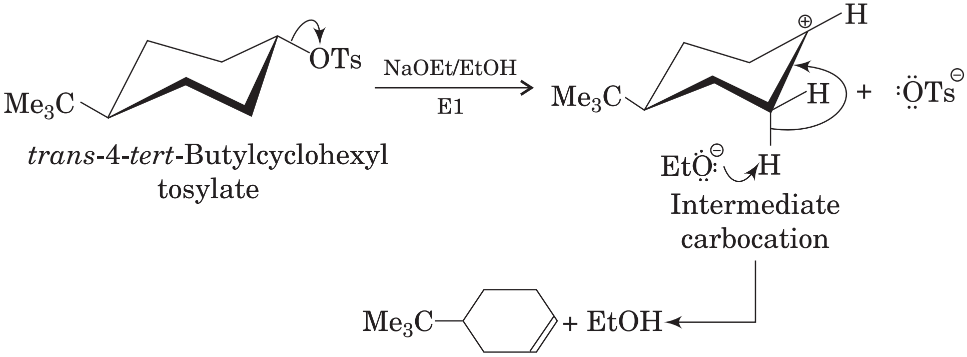
On the other hand, in the stable equatorial-tosylate conformation of the *trans*-isomer, the –OTs group cannot become coplanar with a *β*-H atom (either at C-2 or at C-6), i.e., in this conformation, the stereoelectronic requirement is not fulfilled. Although the stereoelectronic requirement is fulfilled in the energetically very unfavourable axial-tosylate conformation, flipping to this conformation suffering from strong 1,3-diaxial interactions does not practically take place. For these reasons, the *trans*-isomer does not undergo E2 reaction under the same reaction conditions. Slow elimination does take place, but by a unimolecular (E1) mechanism.



(energetically very unfavourable conformation but suitable for E2)

(energetically very favourable conformation but unsuitable for E2)

trans-4-*tert*-Butylcyclohexyl tosylate

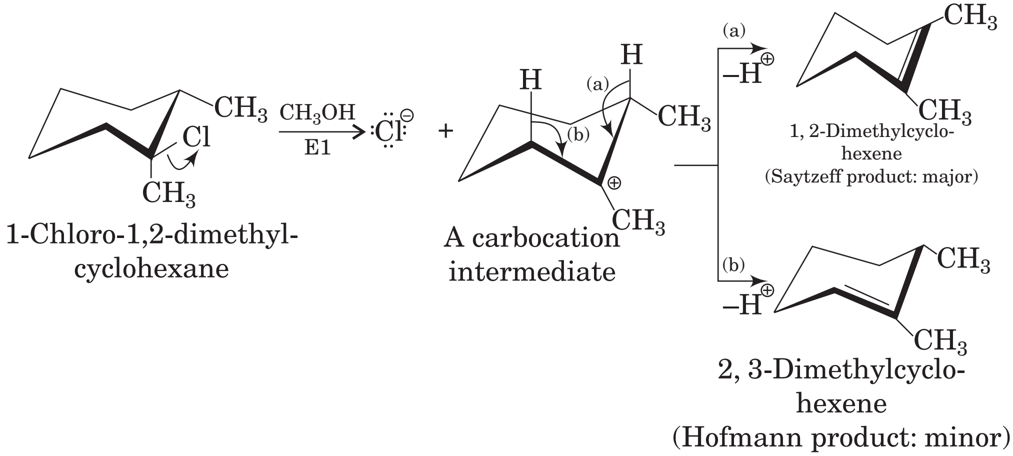


trans-4-*tert*-Butylcyclohexyl tosylate

Intermediate carbocation

4-*tert*-Butylcylohexane

(b) E1 reaction When a substituted cyclohexane undergoes an E1 reaction, the two groups that are eliminated do not have both to be in axial positions because the elimination reaction is not concerted. The carbocation formed in the first step loses a proton to yield the Saytzeff product predominantly. For example, 1-chloro-1,2-dimethylcyclohexane undergoes E1 reaction in methanol to yield 1,2-dimethylcyclohexene (the Saytzeff product) predominantly.



1-Chloro-1,2-dimethyl-cyclohexane

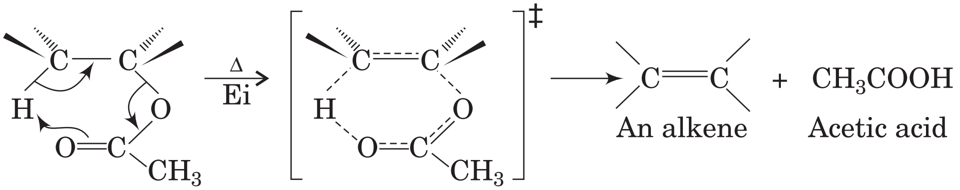
A carbocation intermediate

1, 2-Dimethylcyclohexene (Saytzeff product: major)

2, 3-Dimethylcyclohexene (Hofmann product: minor)

(c) Pyrolylic *syn*-eliminations

1. Pyrolysis of acetates The pyrolytic elimination of an acetate containing at least one β-H atom proceeds concertedly through a six-membered cyclic transition state. The cyclic pathway required a *syn*-coplanar arrangement of the departing groups and so, the reaction is a highly stereoselective *syn*-elimination. The stereochemical course and the mechanism of this intramolecular E2 reaction may be shown as follows:



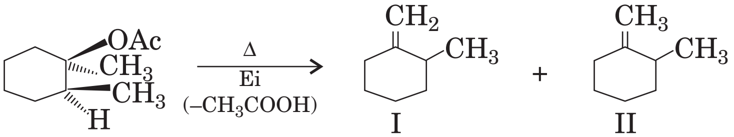
An acetate

Six-membered cyclic transition state

An alkene

Acetic acid

When there are two possibilities of such intramolecular elimination, the major product is that which is obtained through a more stable transition state. The following acetate, for example, undergoes pyrolytic *syn*-elimination to yield the alkene I as the major product and the alkene II as the minor product.

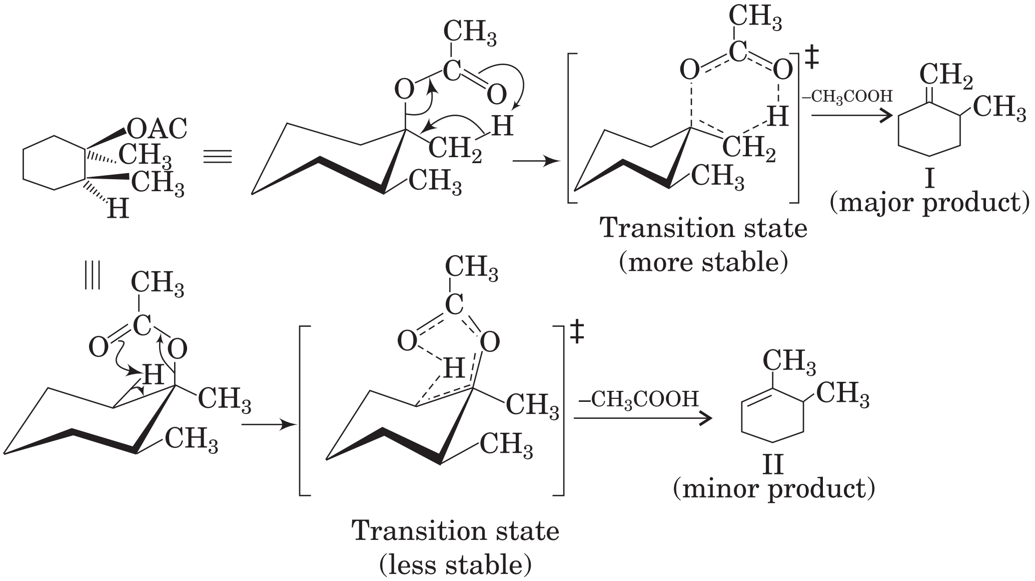


An acetate

I (major product)

II (minor product)

The six-membered cyclic transition state leading to the formation of I is planar and geometrically as well as thermodynamically more favourable, while the six-membered cyclic transition state leading to II is not planar (C—O and βC—H bonds are not coplanar) and thermodynamically less favourable.



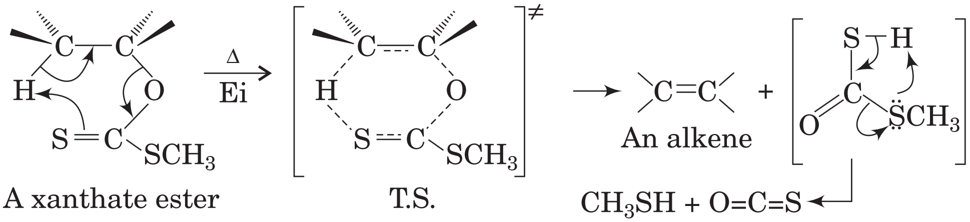
Transition state (more stable)

I (major product)

Transition state (less stable)

II (minor product)

2. Pyrolysis of Xanthates Pyrolysis of xanthate esters to alkenes is known as the *Chugaev reaction*.

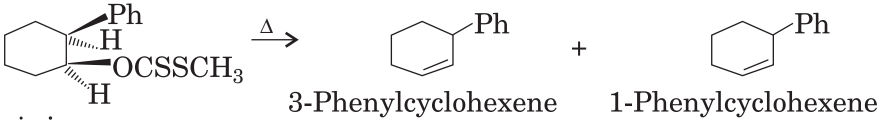


A xanthate ester

T.S.

An alkene

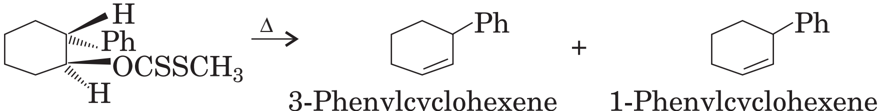
When the *cis*- and *trans*-isomers of the following xanthate esters are heated, 3-phenylcyclohexene and 1-phenylcyclohexene are, respectively, obtained as the major product.



cis-isomer

3-Phenylcyclohexene (96%)

1-Phenylcyclohexene (4%)

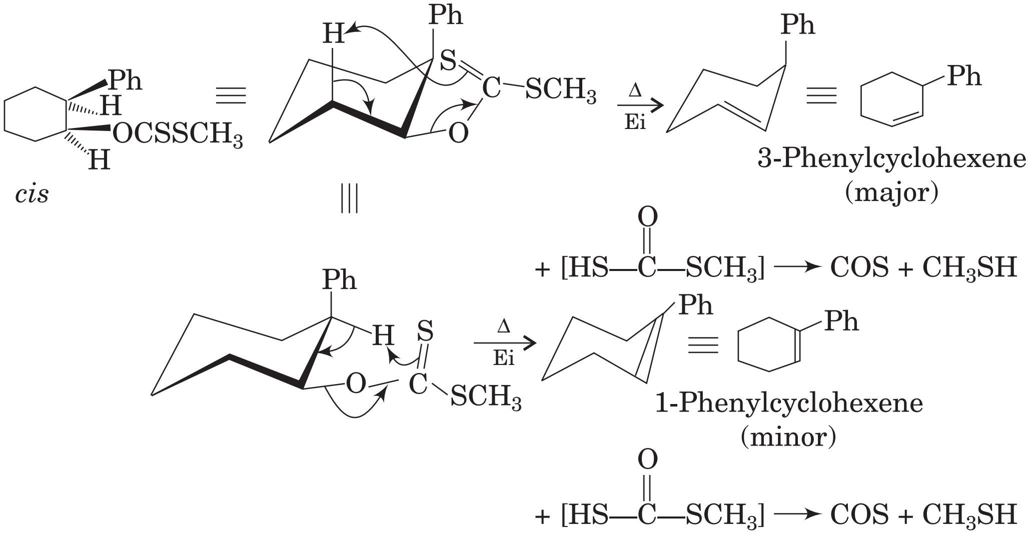


trans-isomer

3-Phenylcyclohexene (12%)

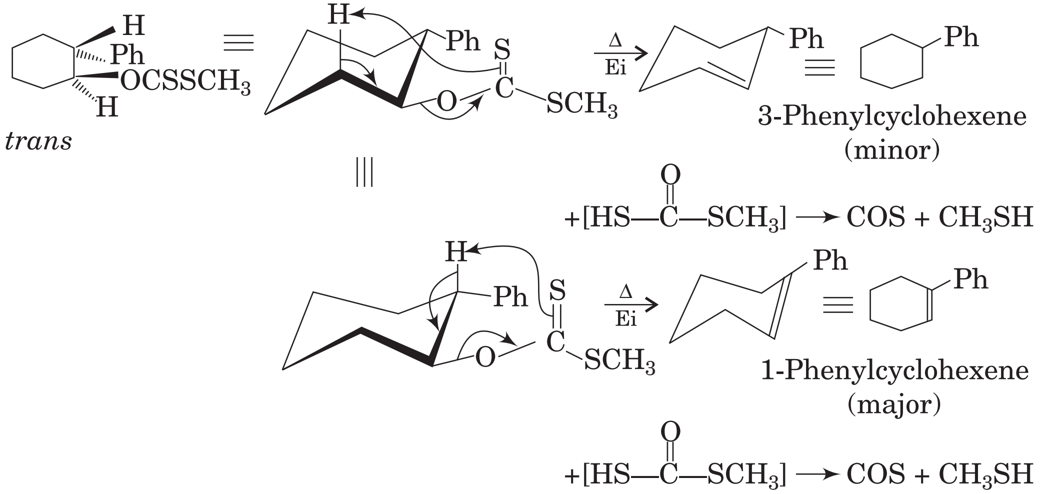
1-Phenylcyclohexene (88%)

In the *cis*-isomer of the xanthate ester, the axial β-H possesses *syn* relationship (e, a) with the –OCSSCH$_3$ group. So, it undergoes Ei reaction through a low-energy transition state to give 3-phenylcyclohexene as the major product. Because of the *anti* relationship (e, e) of the group –$OCSSCH_3$ with the equatorial β-H on the other side, the transition state energy of the corresponding Ei reaction is much higher and so, 1-phenylcyclohexene is obtained as the minor product.



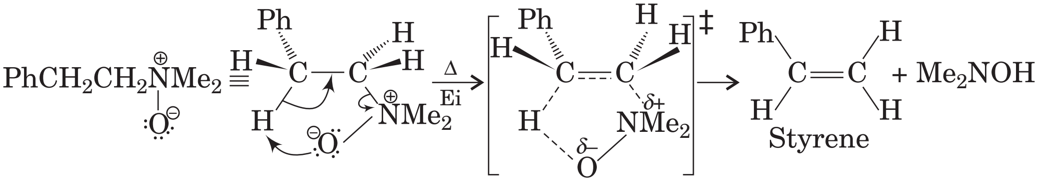
$$+ [HS—\overset{O}{\overset{\|}{C}}—SCH_3] \longrightarrow COS + CH_3SH$$

In the *trans*-xanthate, on the other hand, both of the β-hydrogens possess *syn*-relationship with the –$OCSSCH_3$ group. However, due to the conjugative effect of the phenyl, group, the transition state energy of the reaction leading to 1-phenylcyclohexene is lower than the transition state energy of the reaction lending to 3-phenylcyclohexene. So, 1-phenylcyclohexene is obtained as the major product in this case.



$$+[HS—\overset{O}{\overset{\|}{C}}—SCH_3] \longrightarrow COS + CH_3SH$$

3. Pyrolysis of tertiary amine oxides When tertiary amine oxides containing at least one β-H atom are heated, they undergo decomposition to yield an alkene and a dialkylhydroxylamine. This is what is called the *Cope elimination reaction*. For example:

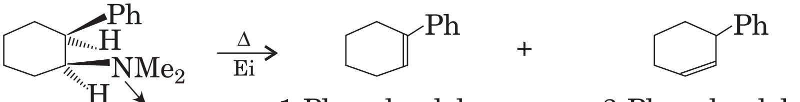


T.S.

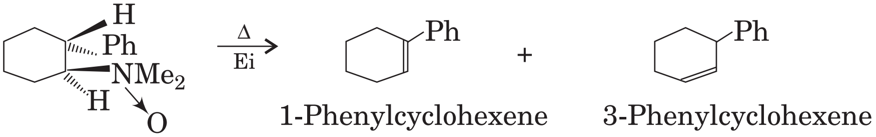
Styrene

In this Ei reaction, the negatively charged oxygen of the amine oxide is the base that removes a proton from the β-carbon. The reaction proceeds through a planar five-membered cyclic transition state. The mechanism of the reaction requires the departing groups to be *syn*-coplanar and in fact, the reaction exhibits the greatest degree of *syn* stereoselectivity of any of the Ei reactions.

That the five-membered cyclic transition state involved in the Cope elimination reaction must be completely planar can be well demonstrated by the reactions of the two isomeric cyclohexyl systems.



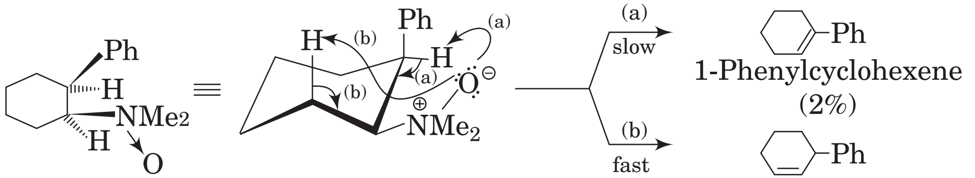
cis-Amine oxide — 1-Phenylcyclohexene (2%) + 3-Phenylcyclohexene (98%)



trans-Amine oxide — 1-Phenylcyclohexene (85%) + 3-Phenylcyclohexene (15%)

Since it is relatively easier to force an axial and an equatorial bond into a plane than two equatorial bonds, therefore, an equatorial and an axial substituent (i.e., *cis* to each other) become involved in pyrolylic *syn* elimination more easily (low activation energy) than two equatorial substituents (i.e., *trans* to each other).

The *cis*-amine oxide undergoes unfavourable *anti*-elimination of the equatorial $-NMe_2 \rightarrow O$ group and the equatorial β-H at C-2 to yield 1-phenylcyclohexene as the minor product. However, it undergoes favourable *syn*-elimination of the equatorial $-NMe_2 \rightarrow O$ group and the axial β-H at C-6 to yield 3-phenylcyclohexene as the major product (almost exclusively).

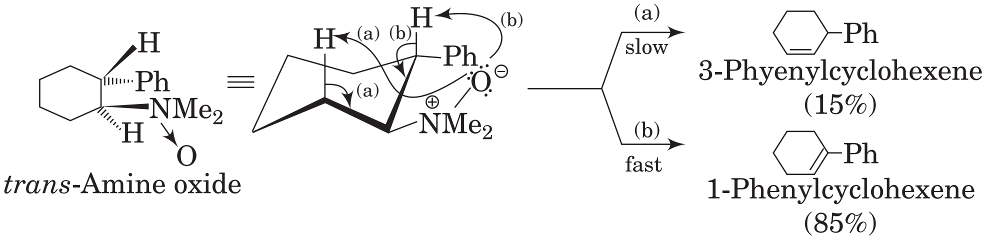


cis-Amine oxide

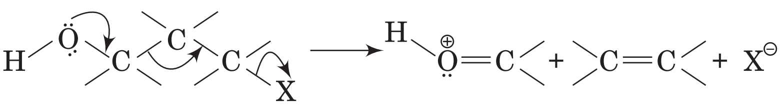
1-Phenylcyclohexene (2%)

3-Phenylcyclohexene (98%)

The pyrolytic elimination of *trans*-amine oxide leading to formation of both 1- and 3-phenylcyclohexene involve a favourable *syn*-elimination of an equatorial $-NMe_2 \rightarrow O$ group and an axial β-H (at C-2 or C-6). An equal amount of both the alkenes is expected to be obtained from this isomer. However, 1-phenylcyclohexene is obtained predominantly and this is because this alkene, being a conjugated one, is thermodynamically more stable than the isomeric 3-phenylcyclohexene.

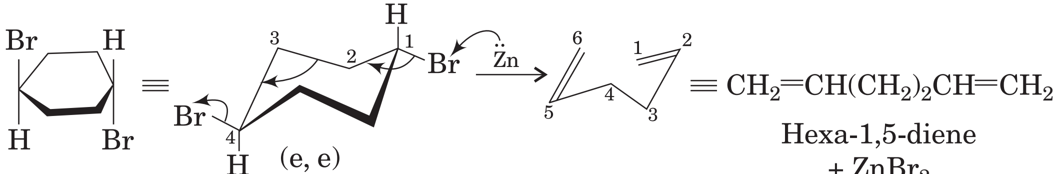


4. Fragmentation reactions Reactions involving cleavage of carbon–carbon bonds are called fragmentation reactions. In such reactions carbon is the positive leaving group (the electrofuge). These reactions take place on substrates of the type W-C-C-X, where X is a normal nucleofuge (e.g., halogen, $\overset{\oplus}{O}H_2$, OTs, $\overset{\oplus}{N}R_3$, etc.) and W is a positive carbon electrofuge. In general, W is $H\ddot{\underset{..}{O}}—C$ or $R_2\ddot{N}—C$, so that the positive charge on carbon is stabilized by the unshared pair of electrons on the oxygen or nitrogen atom. The process may be shown as follows:



The mechanism is mostly E2 or E1.

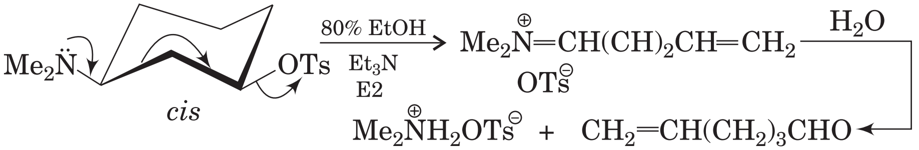
Cyclohexane derivative may also undergo fragmentation reactions. For example, when *trans*-1,4-dibrocyclohexane is treated with zinc, it undergoes fragmentation reaction to yield hexa-1,5-diene. Since in the stable diequatorial conformation of this dibromide, each C—Br bond is *anti* to the C-2—C-3 bond, therefore, it undergoes a facile debromination by zinc accompanied by fission of the C-2—C-3 bond. The stereoelectronic requirement for concerted fragmentation is fulfilled in this case.

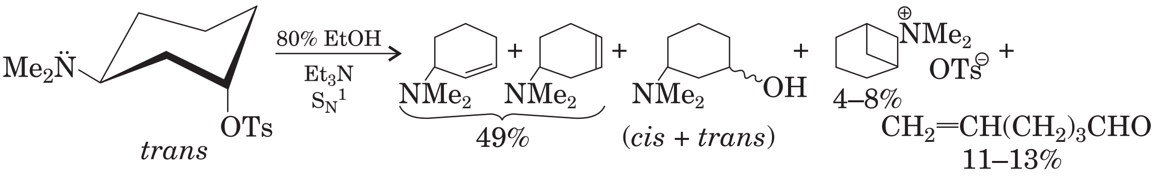


trans-1, 4-Dibromocyclohexane

[Debromination does not take place through the *trans*-diaxial conformation because in that conformation *anti* relationship between the C-2—C-3 bond and the axial C—Br bonds is not maintained, i.e., the stereoelectronic requirement is not fulfilled.]

Another example of the stereoelectronic requirement for concerted fragmentation is given below.

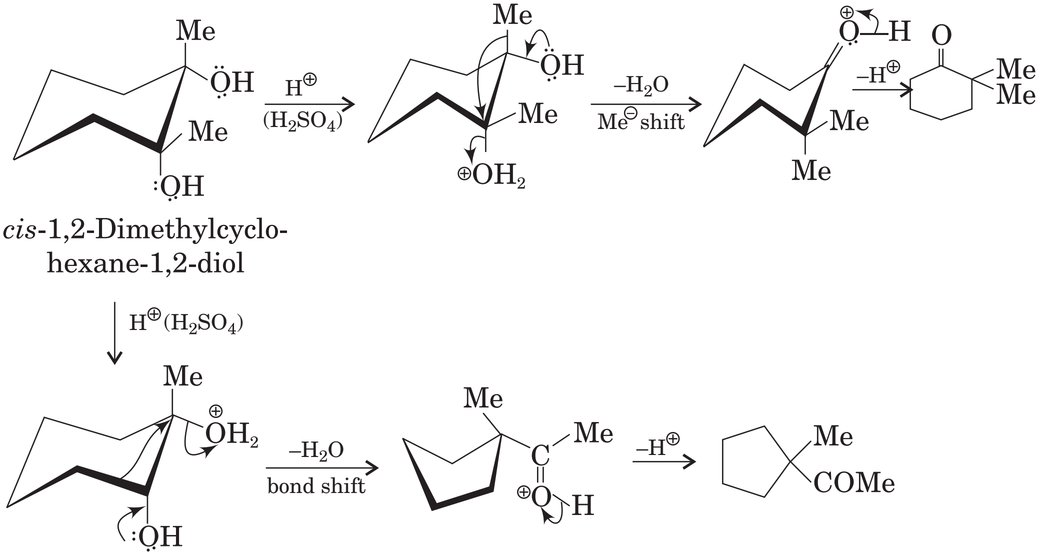


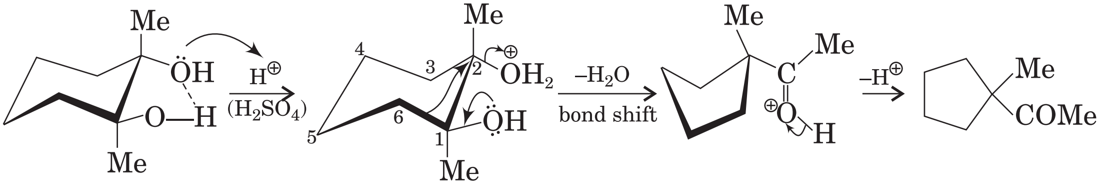


cis-3-Dimethylaminocyclohexyl *p*-toluenesulphonate, upon treatment with triethylamine in 80% EtOH, fragments rapidly to yield the hydrolysis product of the imminium salt. In contrast the *trans*-isomer, which is not properly disposed stereoelectronically for fragmentation, gives mainly solvolysis and elimination products. It reacts at about one-eighth the rate of the *cis*-isomer.

7.2.3.3 Rearrangements

Pinacol-pinacolone rearrangement This type of rearrangement have been observed in cyclohexane-1,2-diols. The nature of product is found to be dependent on the stereochemistry of the substrate diols. For example, *cis*-1,2-dimethylcyclohexane-1,2-diol undergoes acid-catalyzed pinacol rearrangement to yield a cyclohexanone derivative along with a cyclopentane derivative (the ring-contracted product). On the other hand, the *trans*-isomer undergoes only ring contraction to give the same cyclopentane derivative as the exclusive product. This isomer, because of intramolecular hydrogen bonding, exists almost exclusively in the form in which the two —OH groups are equatorial. Therefore, it reacts through this conformational isomer.


cis-1,2-Dimethylcyclohexane-1,2-diol

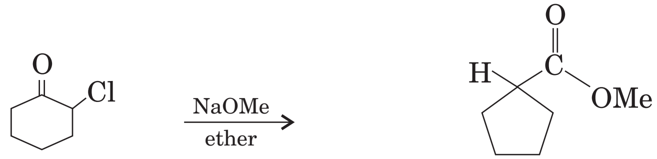


trans-1,2-Dimethylcyclohexane-1,2-diol (OH/OH: e, e)

(C-1–C-6 bond is in *anti*-periplanar orientation with respect to the $–\overset{\oplus}{O}H_2$ group)

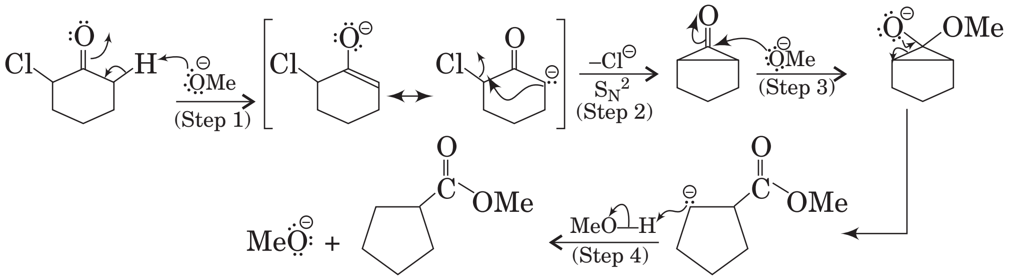
Stereoelectronic effect manipulates the course of the reaction and *anti*-migration is the general rule for pinacol-pinacolone rearrangement.

Favorskii rearrangement Cyclic α-haloketones undergo Favorskii rearrangement to give ring-contracted product. For example when 2-chlorocyclohexanone is treated with NaOMe in ether, methyl cyclopentanecarboxylate is obtained.



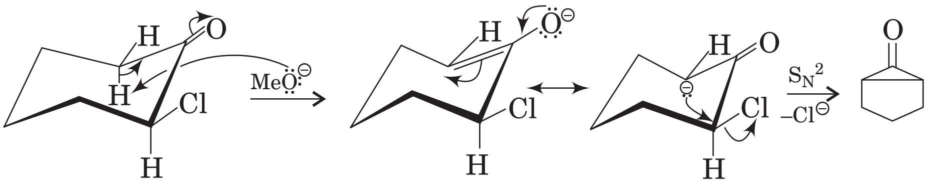
2-Chlorocyclohexanone Methylcyclopentanecarboxylate

The mechanism of the reaction (an anionic rearrangement) involves the steps as follows:



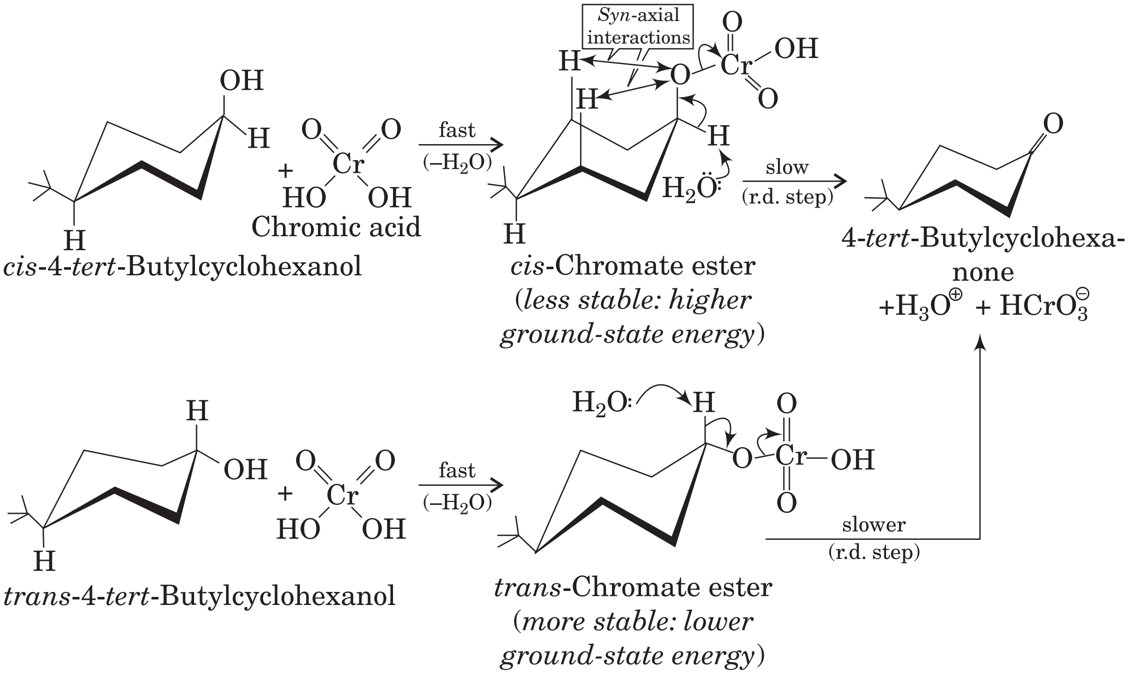
In step 1, an α-H is abstracted by base to form a carbanion. In step 2, intramolecular displacement (S_N2) of the halogen by the α-carbanion takes place to form a symmetrical cyclopropanone intermediate. In step 3, the cyclopropanone ring of the bicyclic ketone is cleaved by the alkoxide ion to form a carbanion which in step 4 abstracts a proton from MeOH to form methyl cyclopentanecarboxylate.

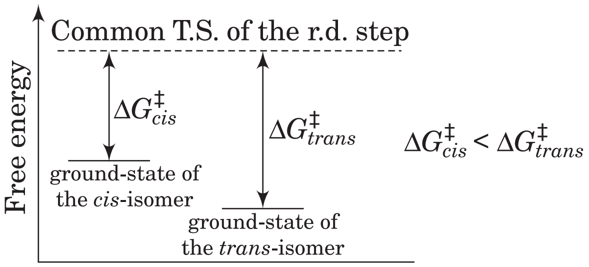
Whether the carbonyl function forms a part of the ring system, the axial hydrogen is abstracted by base preferentially and this is because the σ electrons of the axial bond are more favourably located for overlap with the pi electrons of the carbonyl function. Since the axial hydrogen at C-6 in the starting α-haloketone is *trans* to the equatorial chlorine (*trans*-1,3: e, a), the α-carbanion formed by the expulsion of axial hydrogen is capable of attacking the carbon bearing chlorine from the backside (S_N2).



7.2.3.4 *Oxidations*

Steric assistance or steric acceleration has been observed during oxidation of anancomeric cyclohexanols. The *cis*-isomer of 4-*tert*-butylcyclohexanol undergoes oxidation by chromic acid at a faster rate (approximately four times) than the *trans*-isomer. In this case, the anancomeric (conformationally biased) cyclohexanols give the common oxidation product 4-*tert*-butylcyclohexanone. In the rate determining step, the initially formed chromate ester undergoes loss of H_2CrO_3 (a β-elimination reaction). The *cis*-isomer, which suffers from 1,3-diaxial interactions, undergoes considerable relief of steric strain in the transition state in the process of conversion of chromate ester to ketone. Again, since the transition states involved in the rate-determining step have more product (ketone)-like structure, they may be assumed to have similar energies. Now, because of steric strain, the ground state energy of the *cis*-ester is higher than that of the *trans*-ester. As a consequence, the difference in energy between the ground state and the common transition state, i.e., the activation energy for the *cis*-ester ($\Delta G^{\ddagger}_{cis}$) is less than that for the *trans*-ester ($\Delta G^{\ddagger}_{trans}$) and for this reason, the *cis*-alcohol undergoes oxidation at rate faster than the *trans*-alcohol.



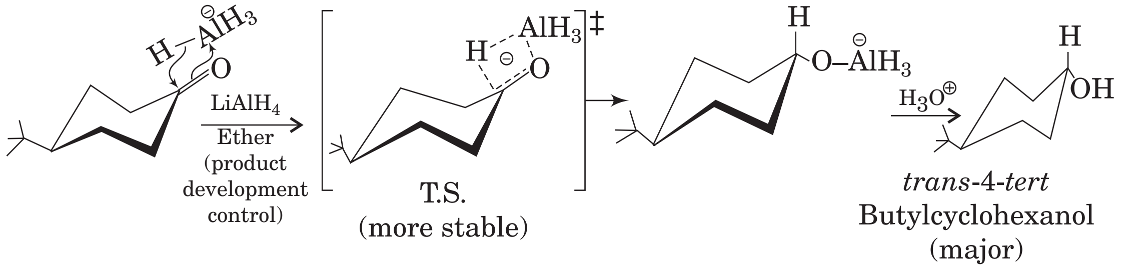

Common T.S. of the r.d. step
Free energy
$\Delta G^{\ddagger}_{cis}$
$\Delta G^{\ddagger}_{trans}$
$\Delta G^{\ddagger}_{cis} < \Delta G^{\ddagger}_{trans}$
ground-state of the *cis*-isomer
ground-state of the *trans*-isomer

7.2.3.5 Reductions

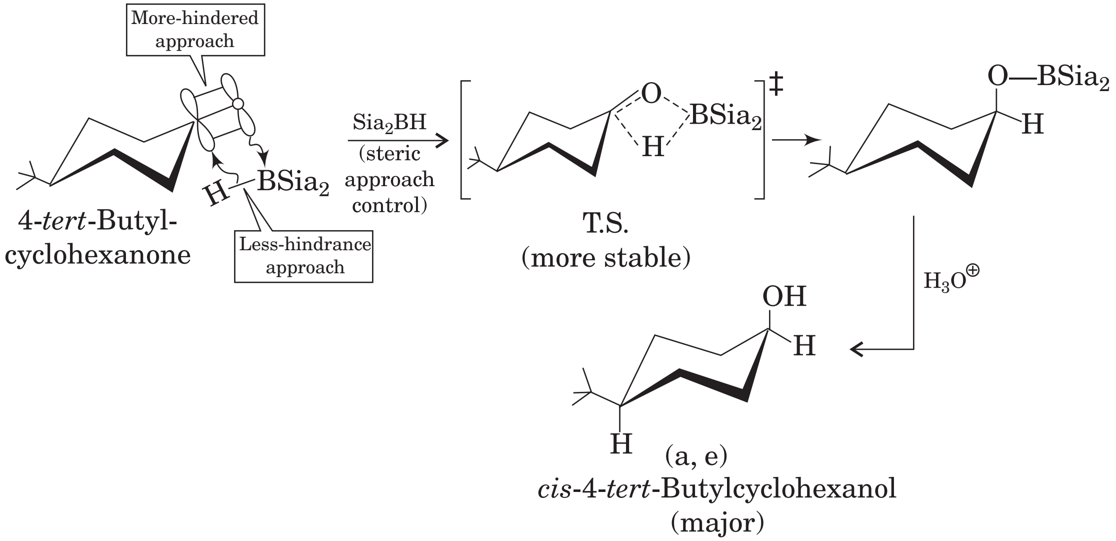
Reduction of cyclohexanone using lithium aluminium hydride ($LiAlH_4$); sodium borohydride ($NaBH_4$), and similar reagents have been studied extensively and a number of important features have emerged. In general, cyclohexanones, hindered sterically by axial substituents at C-3 and C-5, give preferentially the axial alcohol owing to the preferntial approach of the reagent from least hindered equatorial side. This phenomenon is termed as *steric approach control*. However, it is to be noted that the amount of axial alcohol in the product mixture is influenced by the number and size of the axial substituent and size of the reagent used.

The axial mode of attack leading to the equatorial alcohol usually takes place preferably in cyclohexanones having no axial substituents at C-3 and C-5. This phenomenon is termed as *product development control*.

4-*tert*-Butylcyclohexanone is an unhindered ketone because it has no axial substituent at C-3 and C-5 atoms. For this reason, LAH ($LiAlH_4$) reacts with this ketone to yield mainly the thermodynamically more stable equatorial alcohol, i.e., the *trans*-alcohol (*product development control*).

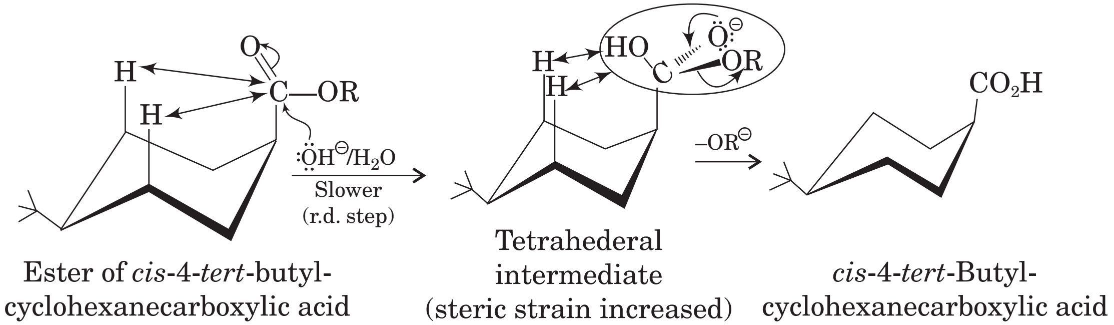


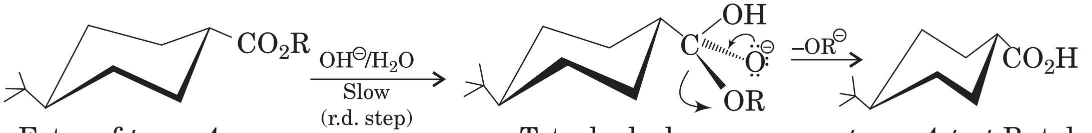
Disiamylborane (Sia_2BH or R_2BH, where R = —$CHMeCHMe_2$) containing two bulky —$CH(Me)CHMe_2$ groups is a hindered reducing agent. For this reason, it becomes involved in steric interaction with the axial hydrogens at C-3 and C-5 in an axial approach. To avoid the steric interaction in axial approach, the reagent attacks the C=O group preferably from the less-hindered equatorial side to yield the thermodynamically less stable axial alcohol, i.e., the *cis*-alcohol predominantly (*steric approach control*).



7.2.3.6 Hydrolysis

Saponification (alkaline hydrolysis) of esters of cyclohexanecarboxylic acid proceeds through the formation of an intermediate (in the rate-determining step) in which carboxyl carbon atom becomes tetrahedral and therefore, the –COOR group is converted to a more bulkier —C(OH)(OR)O$^{\ominus}$ group. As a consequence, the steric strain (1,3-diaxial interaction) is further increased in the case of *cis*-ester with the —COOR group axial but not in the case of *trans*-ester with the —COOR group equatorial. Therefore, the transition state leading to the formation of *cis*-intermediate is relatively more destabilized. Another factor is that the —C(OH)(OR)O$^{\ominus}$ group is more solvated than the neutral —CO_2R group and consequently, steric strain (*syn-diaxial* interaction) is further enhanced. For these reasons, esters of *trans*-4-*tert*-butylcyclohexane carboxylic acid undergo saponification at a much faster rate than the *cis*-isomer.


H
H
O
C—OR
$:\ddot{O}H^{\ominus}/H_2O$
Slower
(r.d. step)
Ester of *cis*-4-*tert*-butyl-cyclohexanecarboxylic acid
H
H
HO
C
$\ddot{O}^{\ominus}$
OR
Tetrahederal intermediate
(steric strain increased)
$-OR^{\ominus}$
CO_2H
cis-4-*tert*-Butyl-cyclohexanecarboxylic acid



Ester of *trans*-4-*tert*-butylcyclohexanecarboxylic acid

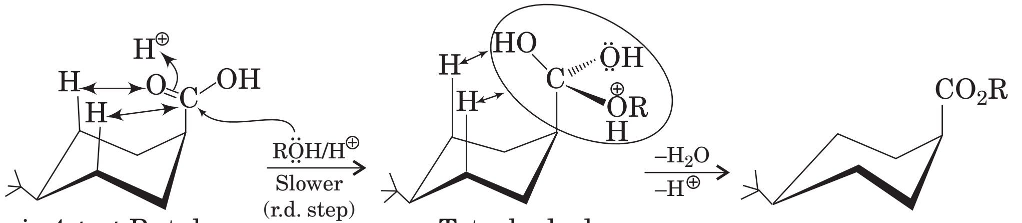
Tetrahedral intermediate (steric strain not increased)

trans-4-*tert*-Butylcyclohexanecarboxylic acid

It is to be noted that the effect of steric interaction on rate is less pronounced when the cyclohexyl substituent is in the alcohol part of the ester and the reason is that the site of crowding (the carbonyl carbon of —COOR group) is not much closer to the ring. In fact, the ester carbonyl is one bond further removed from the cyclohexane ring.

7.2.3.7 Esterification

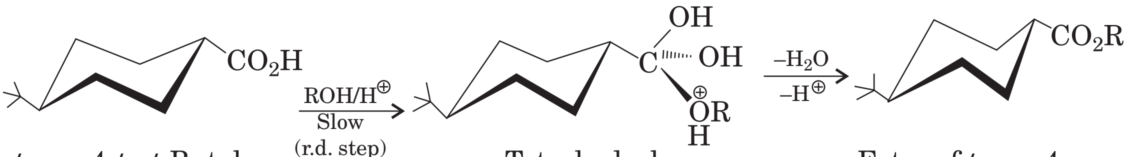
Esterification reaction is just the reverse process of ester hydrolysis. Therefore, the rate of esterification of anancomeric axial and equatorial cyclohexane carboxylic acids will exhibit the same differences as in the case of hydrolysis of esters. Thus, *trans*-4-*tert*-butylcyclohexanecarboxylic acid will undergo esterification reaction at a much faster rate than its *cis*-isomer.



cis-4-*tert*-Butylcyclohexanecarboxylic acid

Tetrahedral intermediate (Steric strain increased)

Ester of *cis*-4-*tert*-Butylcyclohexanecarboxylic acid



trans-4-*tert*-Butylcyclohexanecarboxylic acid

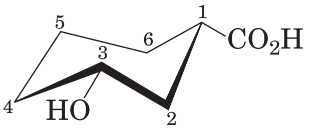
Tetrahedral intermediate (Steric strain not increased)

Ester of *trans*-4-*tert*-Butylcyclohexanecarboxylic acid

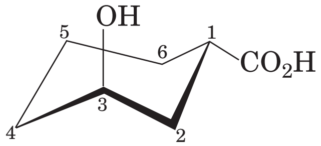
7.2.3.8 Lactonization

When a —COOH group and an —OH group present in a cyclohexane ring come very close to each other, an intramolecular esterification reaction (lactonization) occurs on heating the substrate.

cis-3-Hydroxycyclohexanecarboxylic acid readily forms lactone on heating whereas the *trans*-isomer does not. The more stable conformation of the *cis*-acid is that in which the two susbstituents are equatorial and the more stable conformation of the *trans*-acid is that in which the bulkier —COOH group is equatorial and the —OH group is axial.

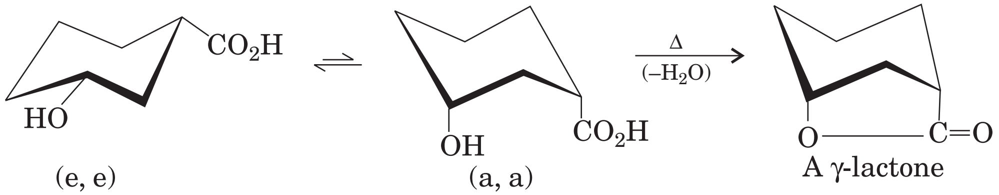


(e, e)
cis-3-Hydroxycyclohexane-carboxylic acid



trans-3-Hydroxycyclohexane-carboxylic acid

The *cis*-acid undergoes ready lactonization on heating through ring inversion process. In the flipped conformation, both the —COOH and —OH groups assume *syn*-diaxial positions and come much closer to each other (within reacting distance) to give a lactone (cyclic ester). Although the inverted conformation is sterically unfavourable (due to 1,3-diaxial interactions), the reaction is favourable from the standpoint of entropy.

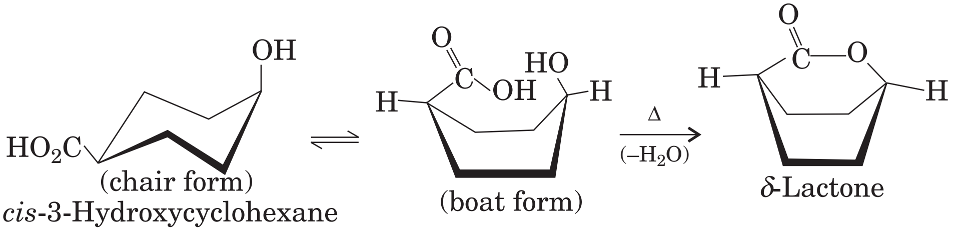


cis-3-Hydroxycyclohexanecarboxylic acid

The *trans*-acid, on the other hand, cannot form a lactone on acid because the —COOH and —OH groups are far apart (beyond reacting distance) from each other, even after ring-flip.

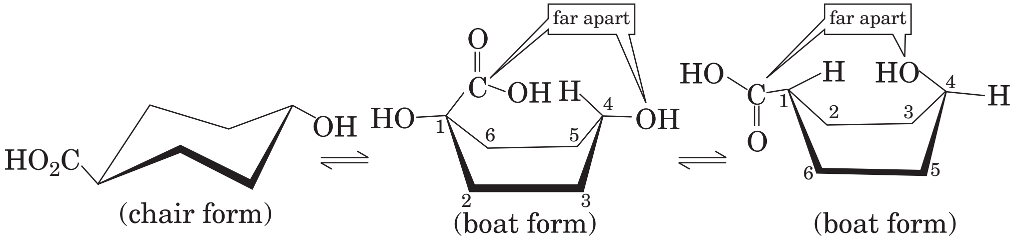
If the —COOH and —OH group in a cyclohexane system come close to each other in a boat conformation, lactonization occurs through this conformation also.

cis-4-Hydroxycyclohexane carboxylic acid lactonizes readily on heating because in its boat conformation the —COOH and —OH groups assume flagpole positions and come within the reacting distance.



cis-3-Hydroxycyclohexane
-carboxylic acid

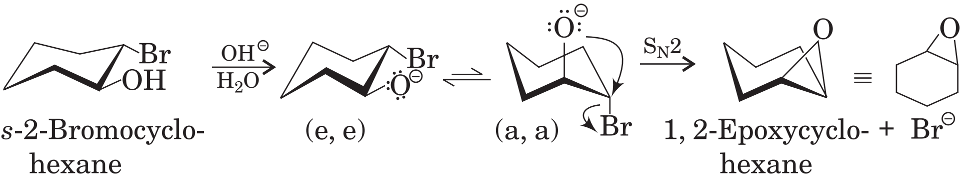
On the other hand, in the boat conformation of the *trans*-isomer only one of the —COOH and —OH groups can assume flagpole position and as a consequence, they do not come within the reaching distance. Because of this, loss of water, i.e., lactonization does not take place on heating the compound.



trans-4-Hydroxycyclohexanecarboxylic acid

7.2.3.9 Conversion of halohydrins to epoxides

Cyclohexane-halohydrins undergo facile ring closure to form epoxides (an intramolecular variation of the Williamson ether synthesis) when the groups involved are both axial. In fact, in diaxial conformation, the stereoelectronic requirement for S_N2 attack is fulfilled. As in other nucleophilic substitutions, the internal nucleophile approaches carbon from the side opposite the bond to the leaving group. *trans*-2-Bromocyclohexanol, for example, must undergo ring inversion before ring formation.



Even though the diaxial conformation of the halohydrin is relatively less stable (due to 1,3-diaxial interactions) than the diequatorial conformation, the two conformation are in rapid equilibrium. As the diaxial conformation reacts to yield the epoxide, it is replenished by the rapidly established conformational equilibrium.

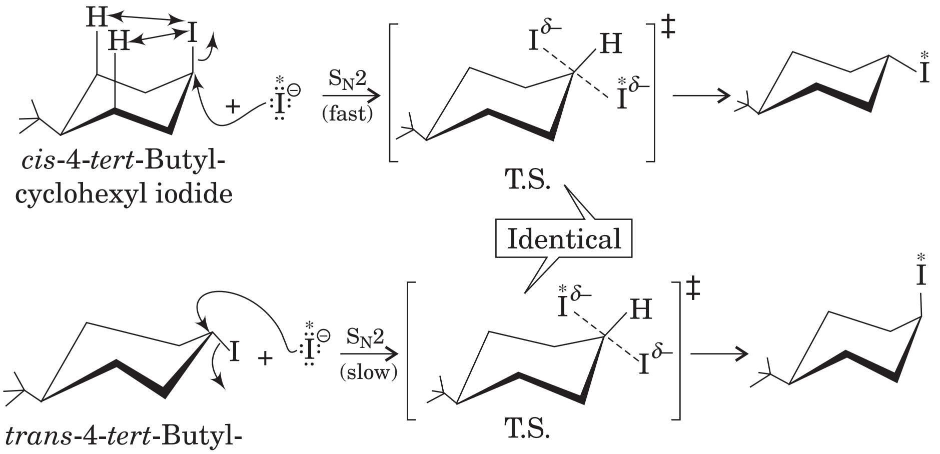
The *cis*-isomer of this halohydrin, on the other hand, is relatively unreactive and does not give an epoxide and this is because the stereoelectronic requirement cannot be fulfilled in this case.

SOLVED PROBLEMS

1. **The *cis*-isomer of 4-*tert*-butylcyclohexyl iodide reacts with $\overset{*}{I}^{\ominus}$ (an S_N2 reaction) at a rate fatser than its *trans*-isomer. Explain this observation.**

Solution Since the transition state is the same for both the reactions therefore, any difference in reaction rate must be due to the differences in the energy of the starting materials. The *cis*-isomer of 4-*tert*-butylcyclohexyl iodide in which iodine is axial suffers from

1,3-diaxial interactions. So, it is less stable (higher ground state energy) than the *trans*-isomer in which iodine is equatorial. The difference in energy between the transition state and the starting material, i.e., the activation energy, is, therefore, lower for the reaction of the *cis*-isomer compared to the reaction of the *trans*-isomer. For this reason, the *cis*-isomer reacts with $\overset{*}{I}^{\ominus}$ at a rate faster than the *trans*-isomer.

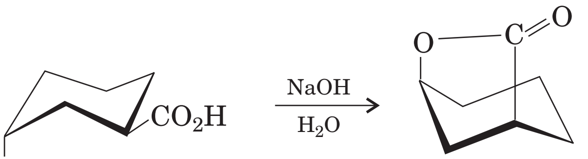


cis-4-*tert*-Butylcyclohexyl iodide

trans-4-*tert*-Butylcyclohexyl iodide

2. Explain the following observations:

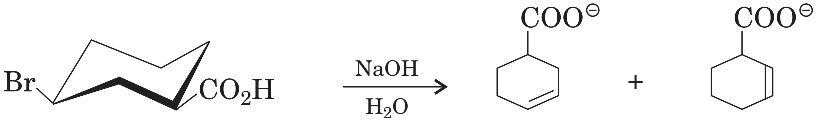
(a)



trans-3-Bromocyclohexanecarboxylic acid

A γ-lactone

(b)

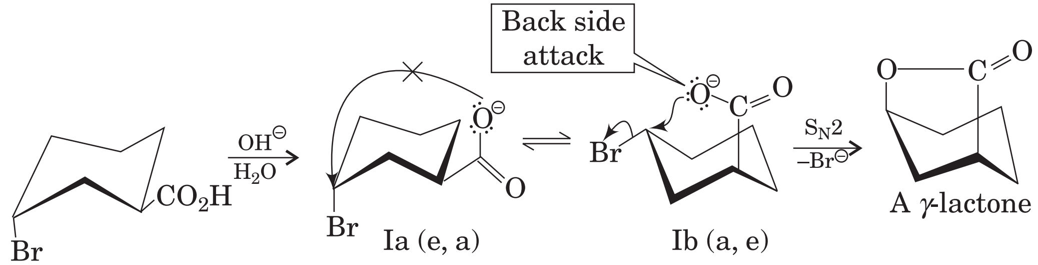


cis-3-Bromocyclohexanecarboxylic acid

Cyclohex-3-en-carboxylate

Cyclohex-2-en-carboxylate

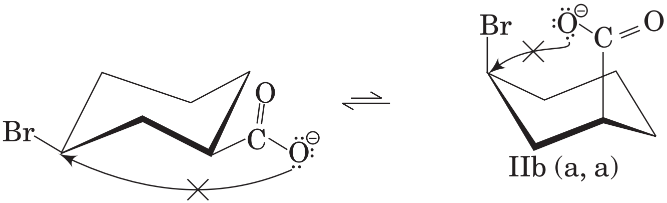
Solution (a) In conformation, Ia (—Br/—$COO^{\ominus}$: a, e) of *trans*-3-bromocyclohexanecarboxylate ion, the —$COO^{\ominus}$ group is not suitably placed to displace bromine from the backside. However, in conformation Ib(—Br/—$COO^{\ominus}$: e, a), the —$COO^{\ominus}$ group is suitably placed to displace bromine by backside attack. Because of this, the compound undergoes an intramolecular S_N2 reaction through the conformation Ib to yield a γ-lactone.



Ia (e, a) Ib (a, e)

trans-3-Bromocyclohexane-carboxylic acid

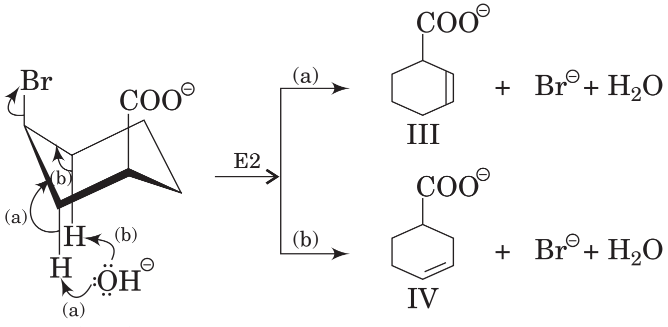
The backside attack is not at all possible in either conformation of the *cis*-isomer (IIa or IIb) because the groups are not placed properly.



IIa (e, e)

cis-3-Bromocyclohexanecarboxylate

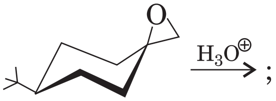
Again, displacement of $Br^{\ominus}$ by $OH^{\ominus}$ in the stable and predominant diequatorial form is not sterically feasible due to *syn-axial* interactions. As a consequence, elimination (E2) reactions occur to yield two isomeric cyclohexenecarboxylate ions (III and IV).



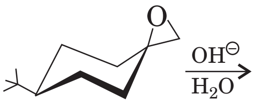
IIb (a, a)

3. Predict the major product in each of the following reactions and give your reasonings:

(a)

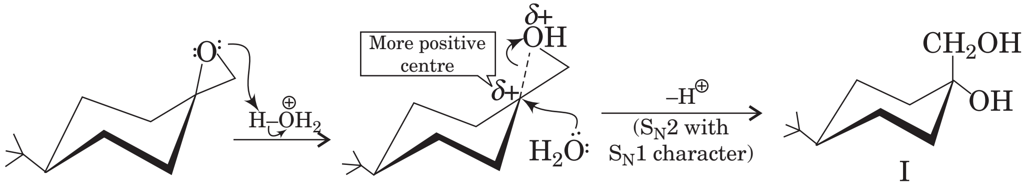


(b)



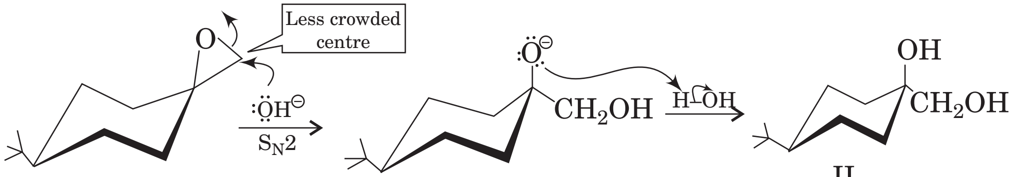
Solution

(a) Under acidic conditions, the bond between the more substituted carbon and the protonated oxygen undergoes cleavage and as a result, the diol I with an equatorial —OH group is obtained as the major product.



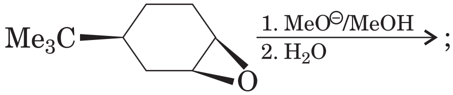
An epoxide

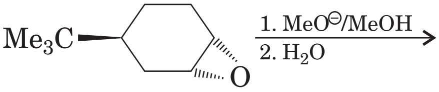
(b) Under alkaline conditions, the cleavage of the epoxide ring occurs purely by the S_N2 mechanism. The nucleophile $OH^{\ominus}$ attacks the less hindered methylene carbon to give the diol II with an axial —OH group as the major product.



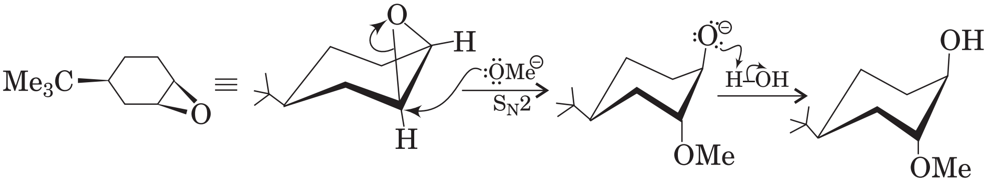
An epoxide

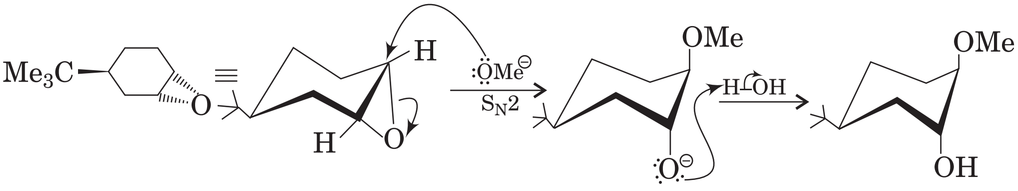
4. Predict the product expected to be formed in each of the following reactions and explain their formations:

(a) 

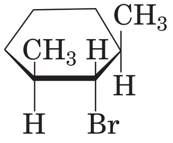
; **(b)** 

Solution Epoxide rings attached to cyclohexane systems are used to open in the *trans* diaxial fashion. Thus, the nucleophile attacks from the axial direction to give a leaving group (the oxyanion) that is also axial. For this reason, only one product is formed in each of the given reactions, even though both ends of the epoxide are equally substituted.

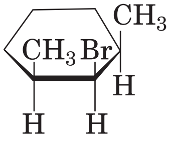
(a) 

(b) 

5. Which of the following two isomeric bromocyclohexanes (A and B) would you expect to be more reactive in an S_N2 reaction and why?

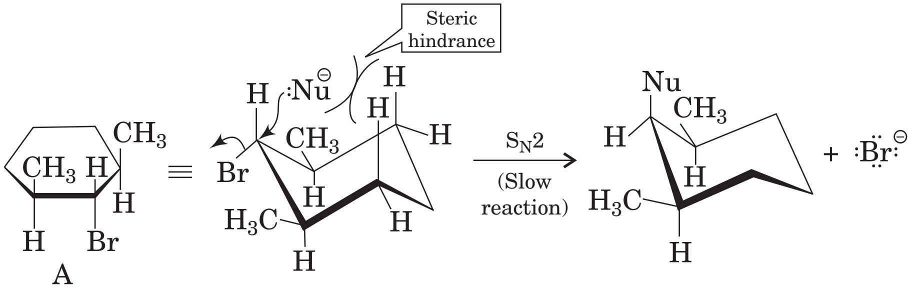


A

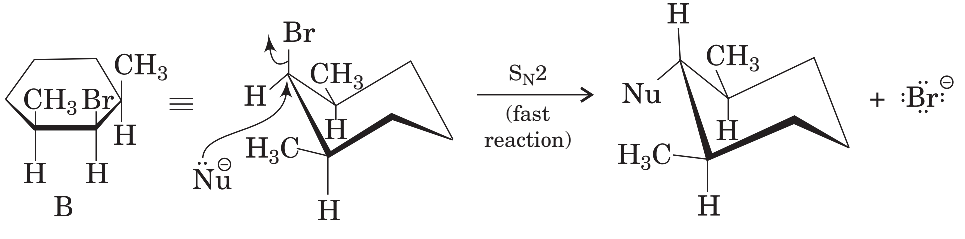


B

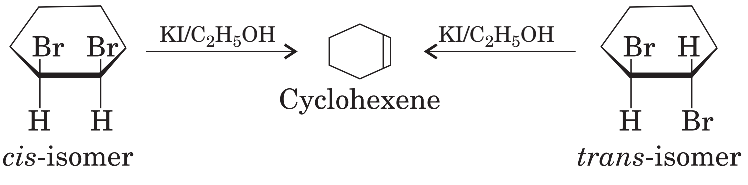
Solution The two relatively bulky methyl groups prefer to exist in the equatorial positions to avoid *syn-axial* interactions. As a consequence, in the more stable conformation of A (through which it reacts), the bromine atom is equatorially oriented. Since the axial approach of a nucleophile for an equatorial leaving group is sterically hindered due to the axial hydrogens at C-3 and C-5 (*syn-axial* interactions), relative to carbon (C-1) undergoing substitution, displacement of bromine takes place very slowly.



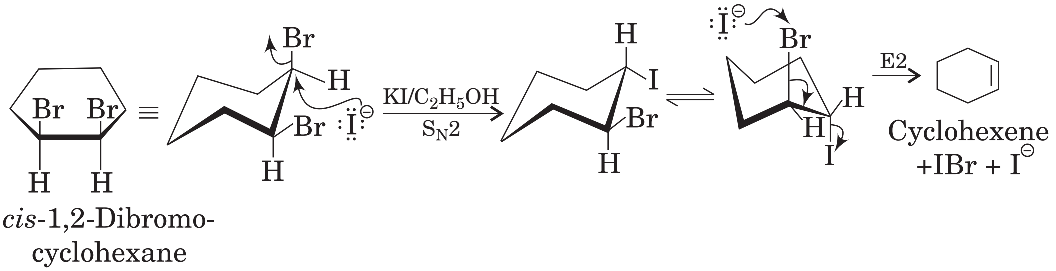
On the other hand, in the more stable, conformation of B (through which it reacts), the bromine atom is axially placed. The equatorial approach of the nucleophile is not sterically hindered and also, the ground state energy of this conformation is higher (i.e., E_{act} is lower) than that of the isomer A. For these reasons, this isomer reacts with the nucleophile by the S_N2 mechanism readily. The bromocyclohexane B is, therefore, more reactive than A in an S_N2 reaction.



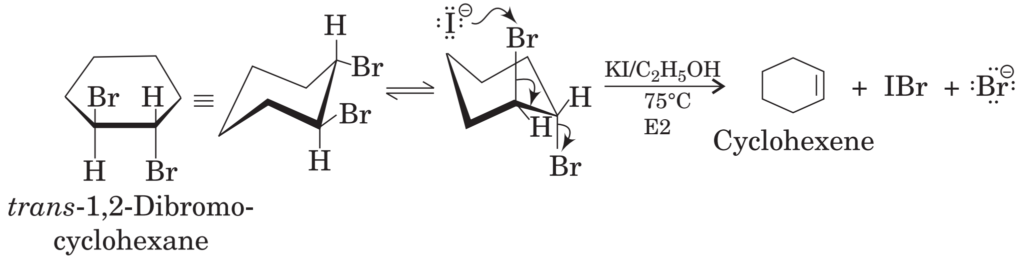
6. Both *cis*- and *trans*-isomers of 1,2-dibromocyclohexane produce cyclohexene when treated with KI in ethanol. Explain these observations.



Solution The *cis*-isomer of 1,2-dibromocyclohexane does not undergo E2 elimination because the two Br atoms are not *anti*-periplanar. However, it yields cyclohexene by a composite S_N2/E2, pathway (a merged substitution-elimination reaction). This debromination thus appears to be a *syn*-elimination.

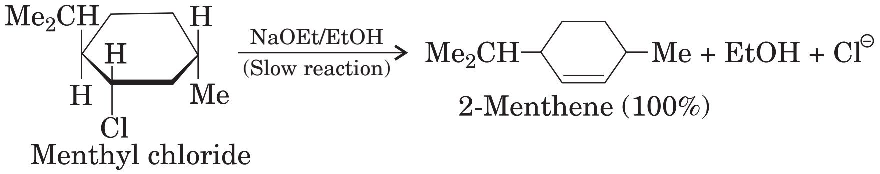


The *trans*-isomer, on the other hand, undergoes debromination caused by I$^{\ominus}$ throng the diaxial conformation (in which the two Br atoms are *anti*-periplanar) to give cyclohexene.

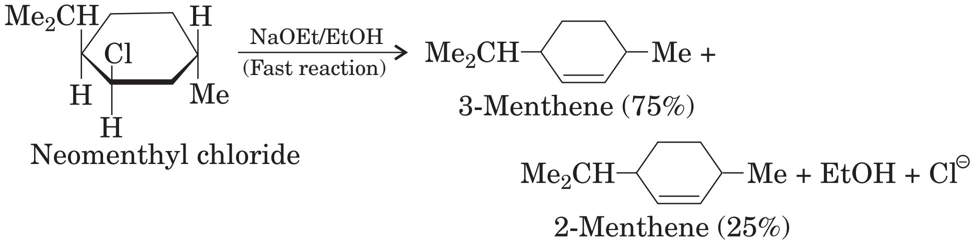


7. Explain the following observations:

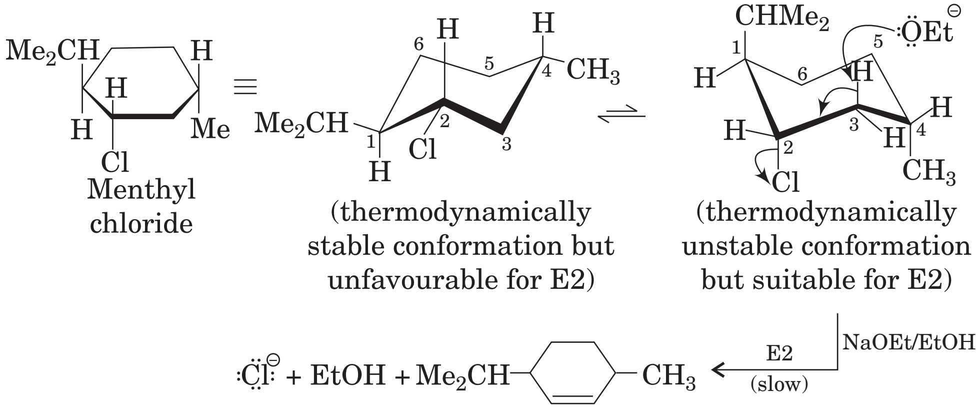
(a)



(b)

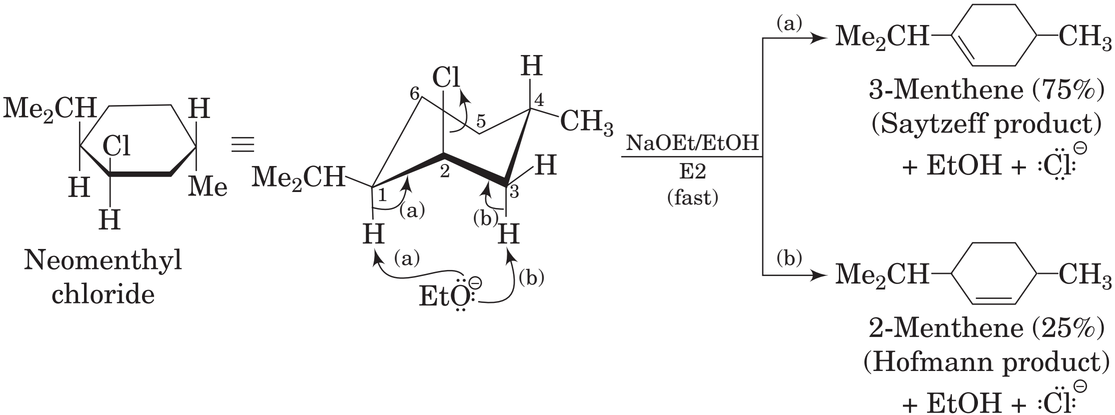


Solution (a) Menthyl chloride exists almost exclusively in the more stable conformation in which all the three substituents are equatorial. For a facile E2 *anti*-periplanar elimination the departing groups in a cyclohexane system must be in axial positions. Thus, for an *anti*-periplanar elimination to take place the ring must flip to the conformation in which all the three substituents are axial. This is a high-energy conformation and the free energy of activation for the reaction is large because it includes the energy required for the ring inversion. For this reason, methyl chloride undergoes E2 dehydrochlorination very slowly. In this conformation, the only axial hydrogen β to the axial chlorine is at C-3. The reaction, therefore, leads to the formation of 2-menthene (the Hofmann product) exclusively.


Me$_2$CH
H
H
H
Me
Cl
Menthyl chloride
≡
6
5
4
H
H
CH$_3$
Me$_2$CH
1
2
3
Cl
H
(thermodynamically stable conformation but unfavourable for E2)
⇌
CHMe$_2$
1
6
5
:ÖEt$^{\ominus}$
H
H
H
H
2
3
H
4
H
Cl
CH$_3$
(thermodynamically unstable conformation but suitable for E2)
NaOEt/EtOH
E2
(slow)
:Cl:$^{\ominus}$ + EtOH + Me$_2$CH
CH$_3$

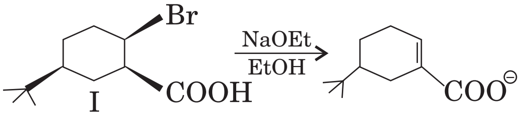
2-Menthene (100%)

In the thermodynamically more stable conformation of neomenthyl chloride, the two relatively bulky alkyl groups are in equatorial position and the chlorine atom is in axial position. There are axial β-hydrogens at both C-1 and C-3. This substrate, therefore, reacts readily with ethoxide ion (EtO$^{\ominus}$) through this energetically favourable conformation (in which the stereoelctronic requirement for E2 reaction is satisfied) to give a mixture of 2- and 3-menthenes. 3-Menthene predominates in the product mixture because it is more substituted and thermodynamically more stable than 2-menthene. The reaction is governed by the Saytzeff rule.

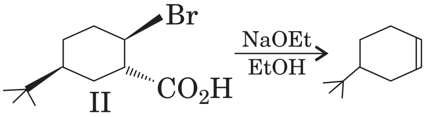


8. Explain the following observations:

(a)

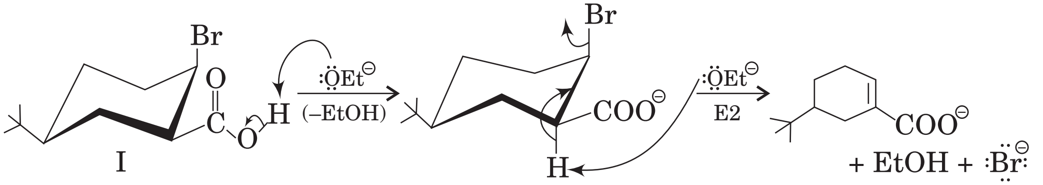


(b)

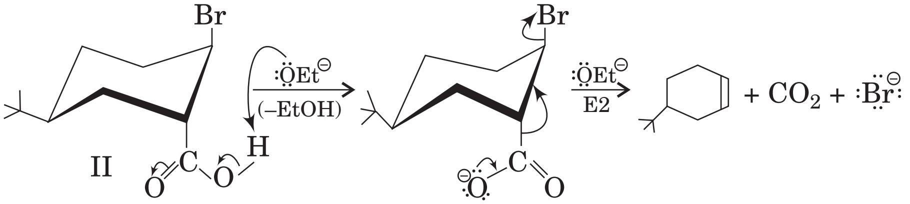


Solution

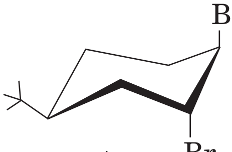
(a) The bulky *tert*-butyl group being an anchoring or holding group holds the smaller substituent Br axial. The compound I, therefore, undergoes dehydrobromination in the presence of base because the stereoelectronic requirement for the E2 reaction is satisfied. An unsaturated acid (salt) is obtained.



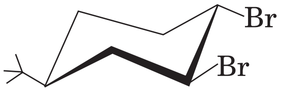
(b) In compound II, the *tert*-butyl group holds both the Br atom and the —COOH group axial. Because of this, it undergoes base-induced decarboxylative debromination to give 4-*tert*-butylcyclohexene.



9. The compound A undergoes debromination in the presence of I$^{\ominus}$ but the isomeric compound B does not. Explain these observations.

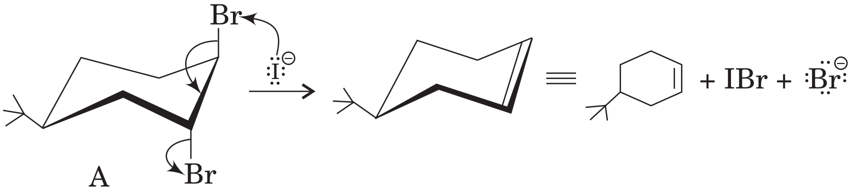


A

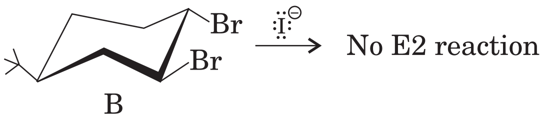


B

Solution In compound A, the *tert*-butyl group (an anchoring or holding group) holds the smaller Br atoms axial. Since the stereoelectronic requirement for the E2 reaction is satisfied in this more stable conformation, the compound undergoes ready debromination in the presence of I$^{\ominus}$.

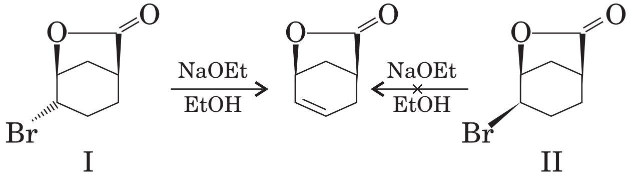


On the other hand, the *tert*-butyl group in compound B holds the two bromine atoms equatorial. Since the stereoelectronic requirement for the E2 reaction is not satisfied in this more stable conformation, the compound does not undergo debromination to yield an alkene.

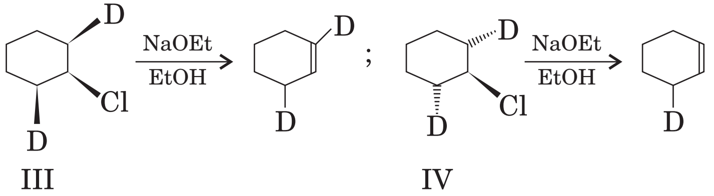


10. Account for the following observations:

(a)

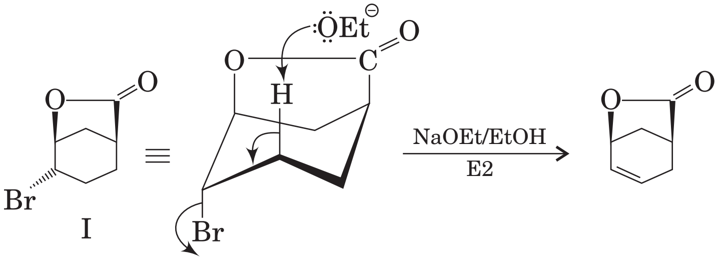


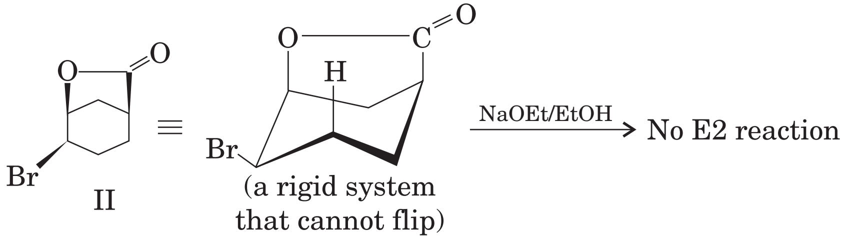
(b)



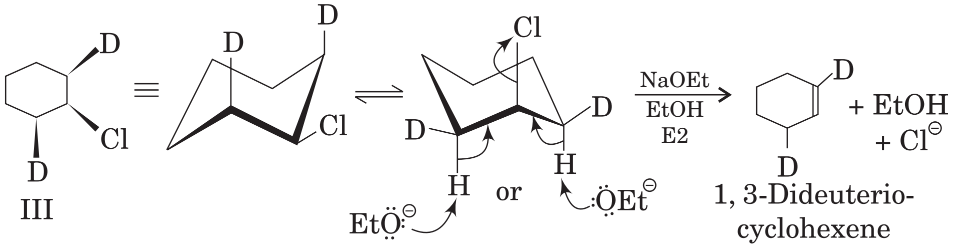
Solution

(a) In lactone I, bromine is axially oriented and there is an axial hydrogen on the adjacent carbon. Therefore, the stereoelectronic requirement for E2 reaction is satisfied in this compound and so, it undergoes facile dehydrobromination in the presence of base. On the other hand, the isomeric lactone II, because of its rigidity, cannot flip to the axial-bromine conformation. Since the stereoelectronic requirement for E2 is not satisfied, therefore, this lactone does not undergo base-induced dehydrobromination.

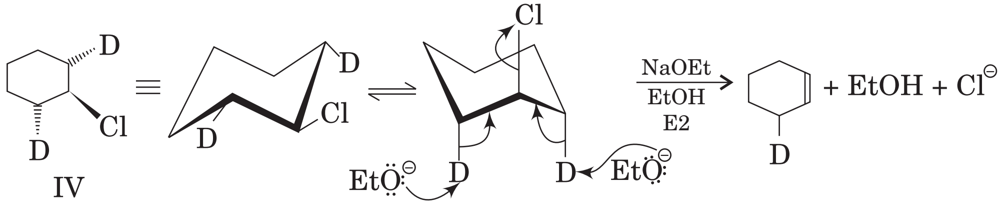




(b) The compound III undergoes base-induced dehydrochlorination (E2) through the conformation in which the Cl atom is axial and *anti*-periplanar with the adjacent axial hydrogens to yield 1,3-dideuteriocyclohexane.

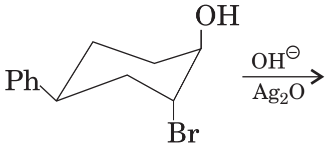


The diastereoisomeric compound IV, on the other hand, undergoes base-induced elimination of DCl to yield 3-deuteriocyohexene because in the axial-chlorine conformations the two adjacent D atoms are also axially oriented.

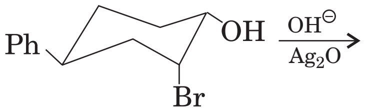


11. Predict the major product in each of the following reactions and explain its formation:

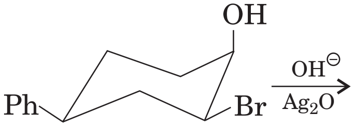
(a)



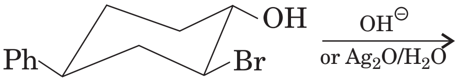
(b)



(c)

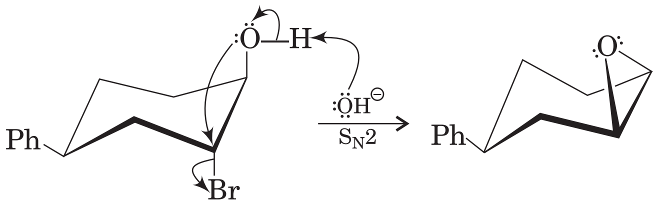


(d)

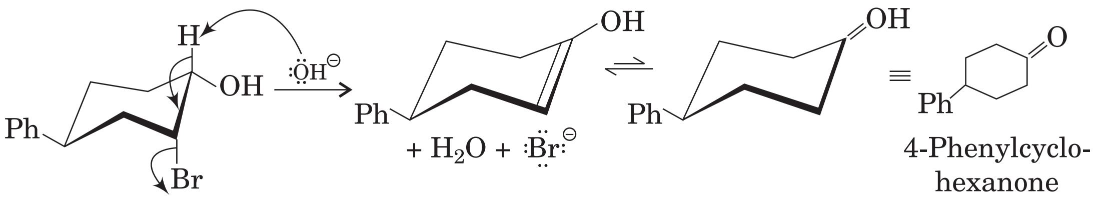


Solution

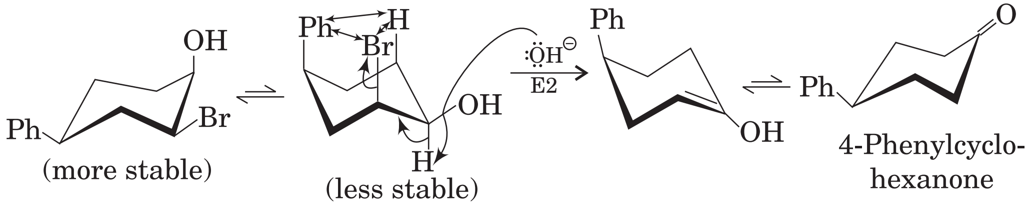
(a) Since —OH and —Br are *anti*-periplanar; therefore, S_N2 type displacement leading to the formation of an epoxide is the preferred reaction in this case. $Ag_2O(Ag^+)$ can also initiate the reaction by co-ordinating with Br atom as a Lewis acid.



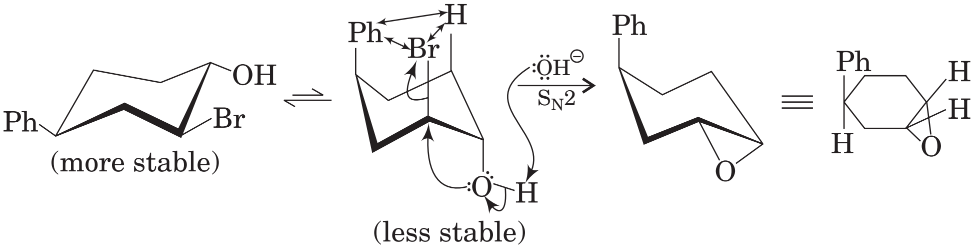
(b) Since H and Br atoms are *anti*-periplanar; therefore, the compound undergoes E2 elimination to yield an enol which readily tautomerizes to the more stable keto form (a cyclohexanone derivative).



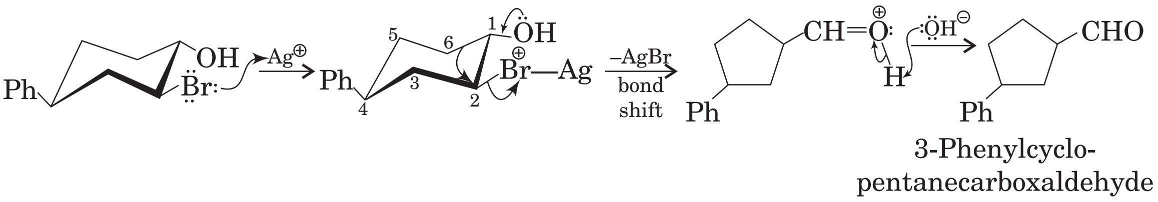
(c) The more stable conformation of the compound has no proper stereoelectronic situation for either epoxide formation (by S_N2 attack) or E2 elimination. Elimination of HBr leading to the formation of 4-phenylcyclohexanone occurs only after ring inversion because in that conformation the stereoelectronic requirement is satisfied. However, the rate of the reaction is slow because the conformation suffers from *syn-axial* interactions.



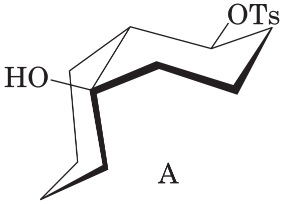
(d) The relatively less stable conformation of this compound undergoes an internal S_N2 reaction in the presence of alkali to yield an epoxide. However, because of *syn*-axial interactions, the reaction is slow.



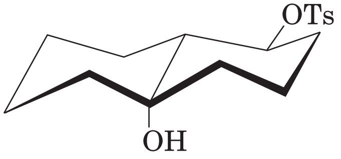
In the presence of $Ag_2O(Ag^+)$, a cyclopentanecarboxaldehyde derivative is obtained by bond migration and this is because $Ag^{\oplus}$ induces the departure of equatorial bromine by acting as a Lewis acid. The C—Br bond is now *anti* to the C-1–C-6 bond.



12. The tosylate A and the tosylate B yield the same product when heated with a base:

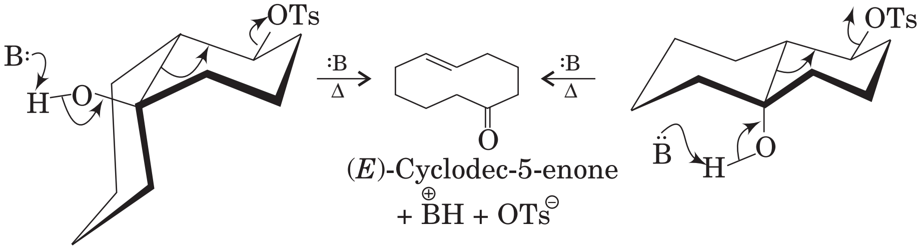


A

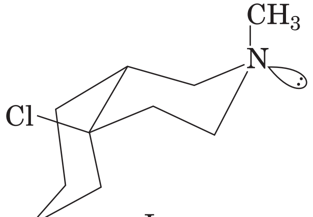


Predict the product and provide reasonable mechanisms for these transformations.

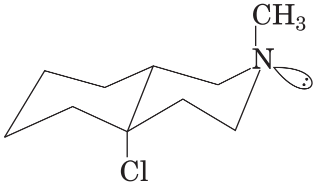
Solution The product is an unsaturated ketone. The fragmentation reactions leading to the formation of this ketone take place as follows:



13. What happens when each of the following heterocyclic ring systems (I and II) are heated?

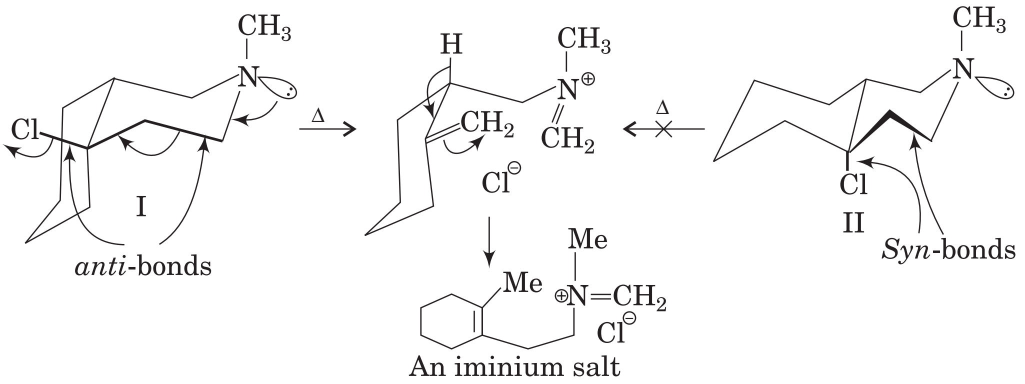


I



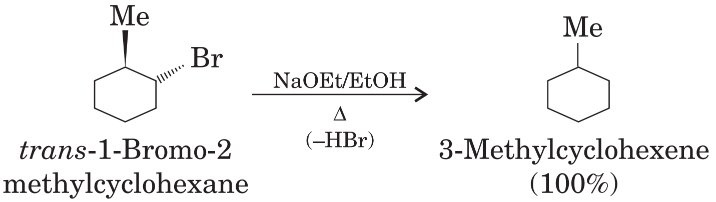
II

Solution Heterocyclic ring systems having chair-like conformation similar to cyclohexane derivative may undergo fragmentation reaction if the stereoelectronic effect is helpful. When the compound I is heated, it undergoes concerted fragmentation reaction because the stereoelectronic effect is now helpful. On the other hand, the compound II does not undergo concerted fragmentation reaction because, due to axial orientation of Cl, there is no favourable stereoelectronic situation.

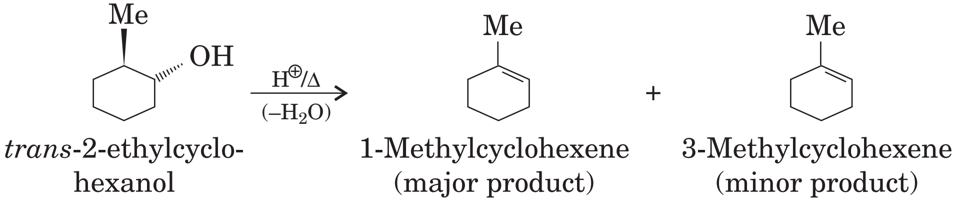


14. Give mechanistic explanation for each of the following observations:

(a)

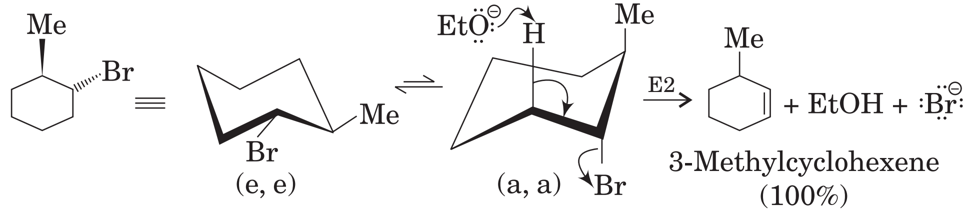


(b)


Me
OH
H⊕/Δ
(–H2O)
Me
+
Me
trans-2-ethylcyclohexanol
1-Methylcyclohexene (major product)
3-Methylcyclohexene (minor product)

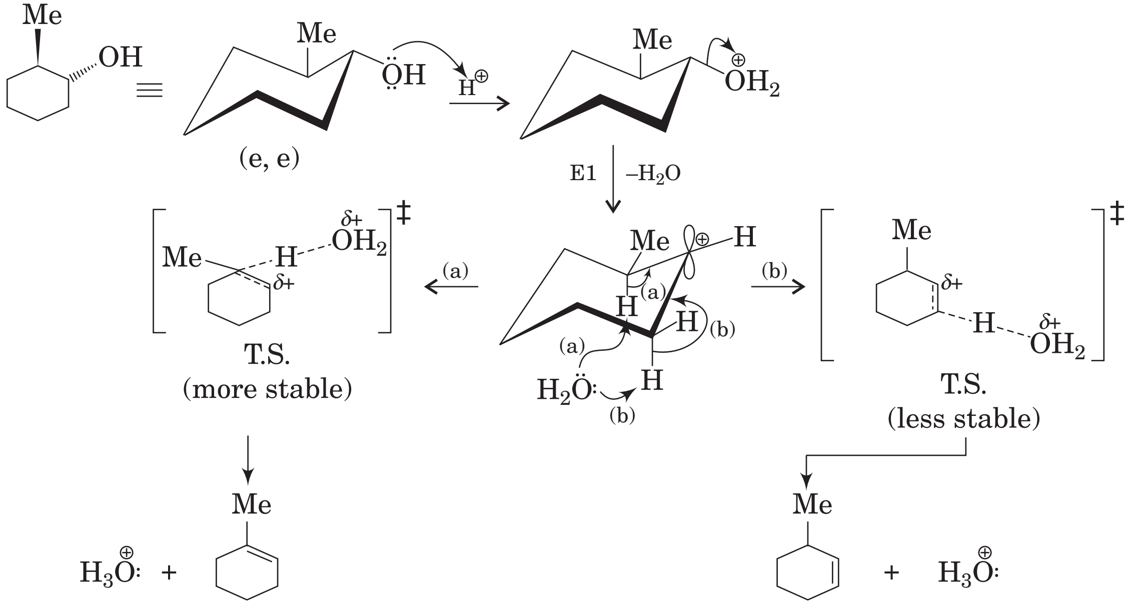
Solution

(a) *trans*-1-Bromo-2-methylcyclohexane undergoes E2 dehydrobromination when it is heated with sodium ethoxide in ethanol. For a facile E2 elimination, the ring must flip to the diaxial conformation in which the departing groups are *anti*-periplanar. Since in this conformation the only axial hydrogen β to the axial bromine is situated at C-6, therefore, the reaction leads to the formation of 3-methylcyclohexene exclusively (100%).



trans-1-Bromo-2-methycyclohexane

When *trans*-2-methylcyclohexanol is heated in the presence of an acid, it undergoes acid-catalyzed dehydration by the E1 mechanism. The alcohol becomes protonated and then loses water to form a carbocation. The carbocation may lose two β-hydrogens (from C-2 to C-6) to form to alkenes. Since the transition state leading to the more substituted alkene (the Saytzeff product) 1-methylcyclohexene is relatively more stable than the transition state leading to the less substituted alkene-3-methylcyclohexene, therefore, the former alkene is obtained as the major product.

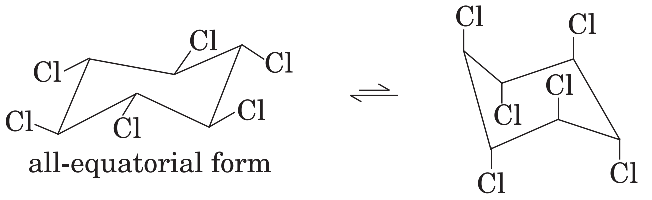


1-Methylcyclohexene
(major product)

3-Methylcyclohexene
(major product)

15. Draw the structure of an isomer of benzene hexachloride which does not undergo E2 dehydrochlorination and explain why it is unreactive.

Solution The (e, e, e, e, e, e) isomer of benzene hexachloride or its conformational diastereoisomer (a, a, a, a, a, a) does not undergo E2 dehydrochlorination when treated with base. This is because in both of these forms, no Cl and H atoms are diaxially oriented, i.e., in none of two forms, the stereoelectronic requirement for the E2 elimination is satisfied.



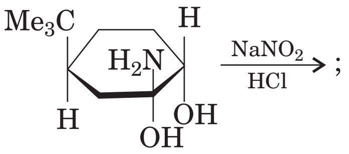
all-equatorial form

all-axial form

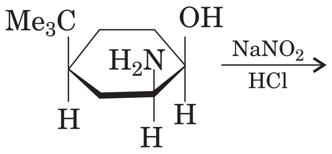
Benzene hexachloride

16. Account for the following observations:

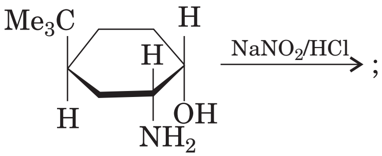
(a)



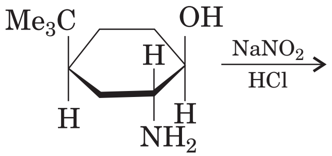
(b)



(c)



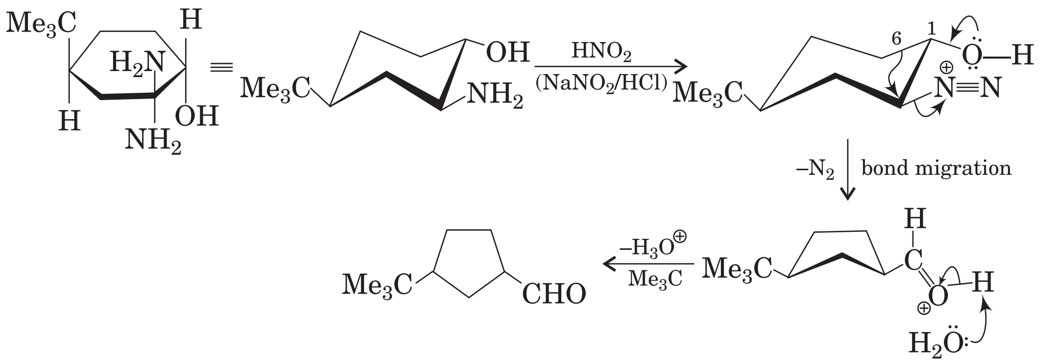
(d)



Solution

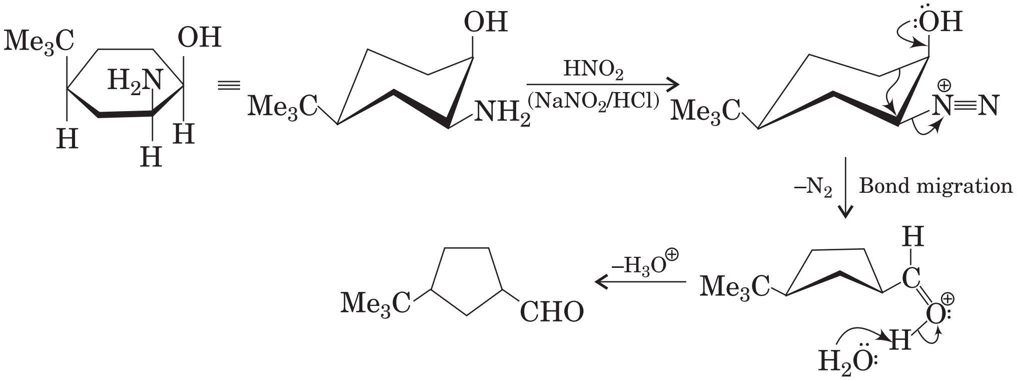
The very bulky —CMe$_3$ group (a 'locking group') hold a molecule nearly exclusively in that particular conformation in which it occupies an equatorial position.

(a)



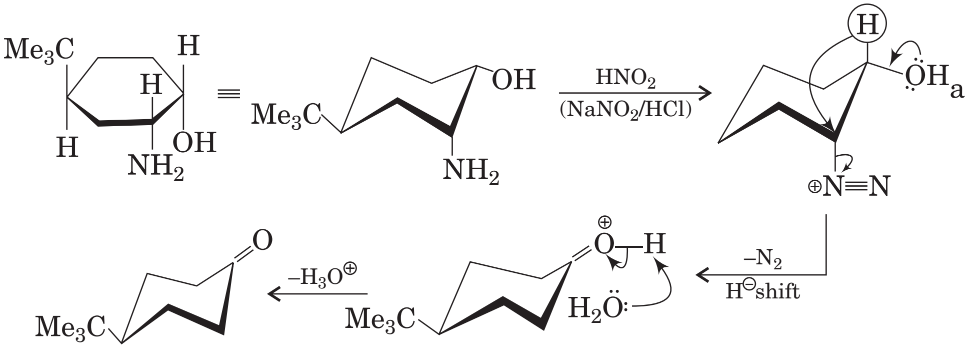
Bond migration occurs because the C-1—C-6 bond is *anti*-periplanar with the $C—\overset{\oplus}{N}_2$ bond.

(b)



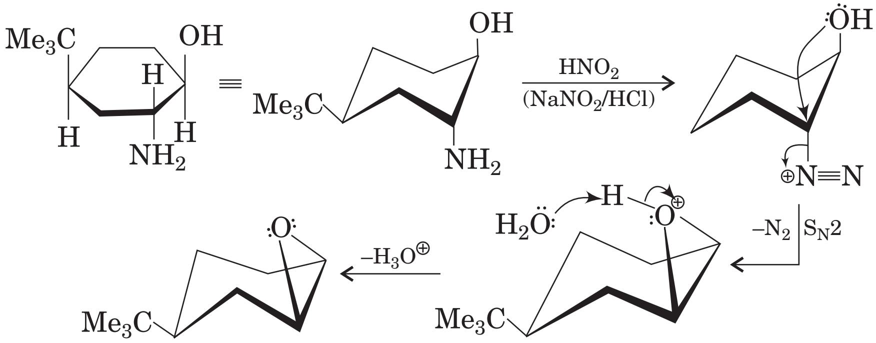
Presence of —OH in the axial position makes no difference in product.

(c)



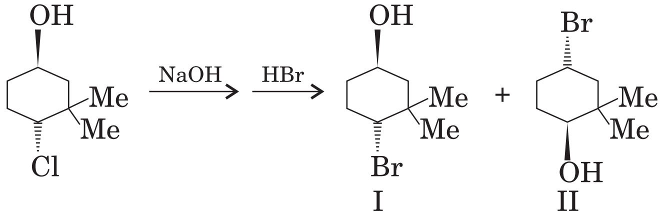
Hydrogen being *anti*-periplanar with resepect to the $—\overset{\oplus}{N}_2$ group migrates to form 4-*tert*-butylcyclohexanone.

(d)



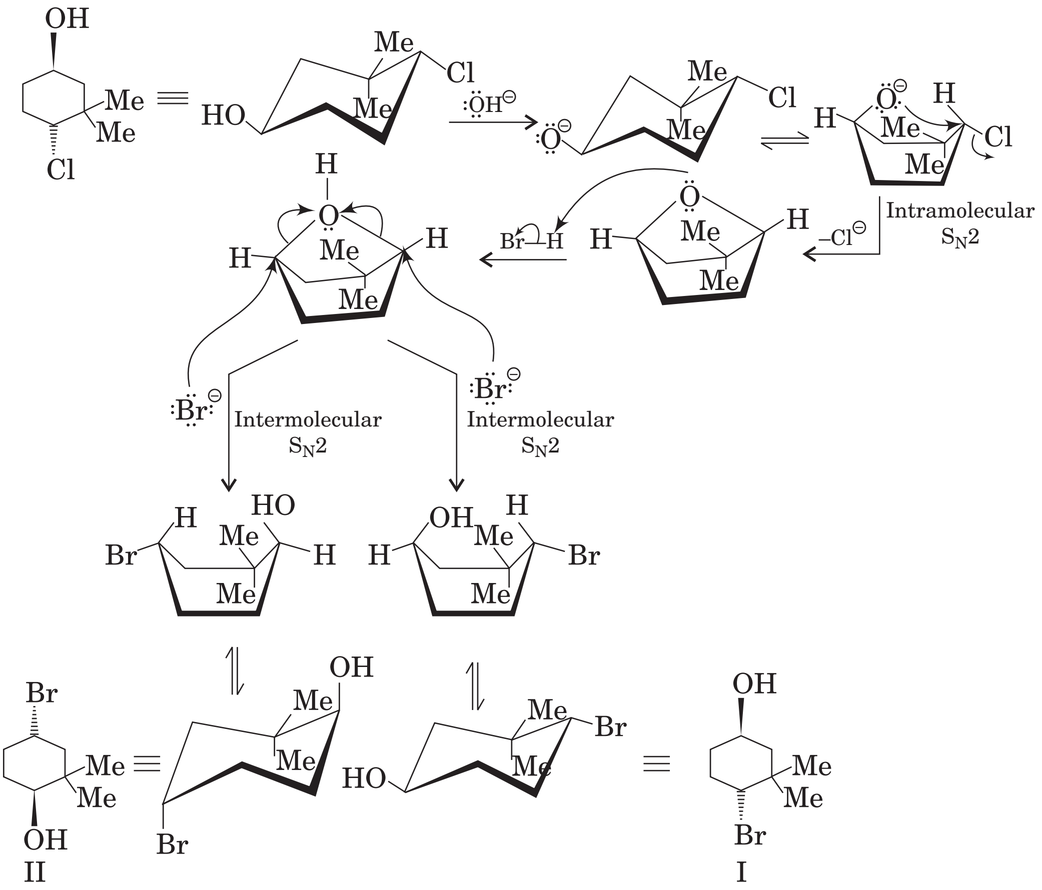
An epoxide is found because the axial —OH group is in proper position for backside attack (S_N2).

17. Propose a reasonable mechanism for the following reaction:



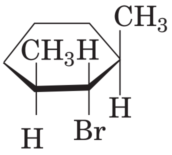
Solution

The reaction proceeds through an intramolecular S_N2 followed by an intermolecular S_N2 to give these two isomeric products (I and II).

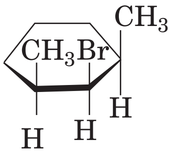


STUDY PROBLEMS

1. Which of the following two isomeric halocyclohexanes (I and II) would you expect to be more reactive in an S_N2 reaction and why?

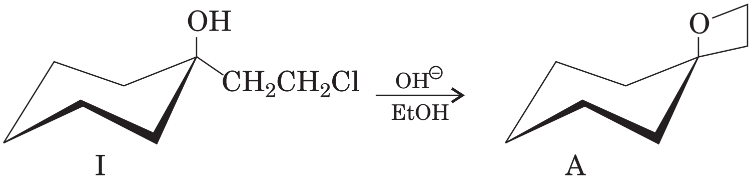


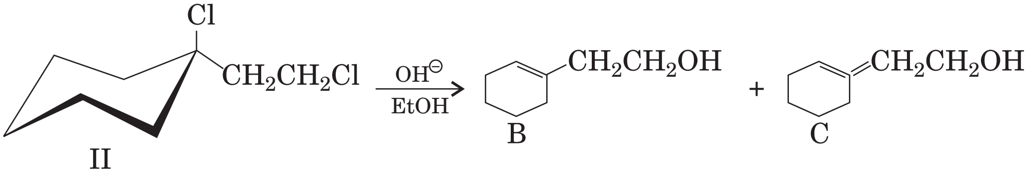
I



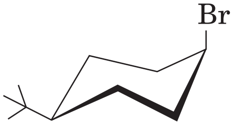
II

2. Explain the following observations:

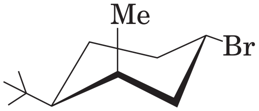




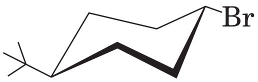
3. Rank the alkyl bromides in order of increasing S_N2 reactivity and give your reasoning:



I

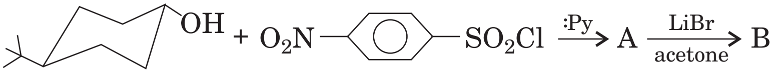


II

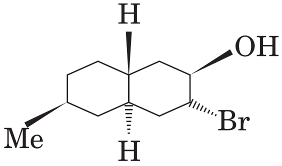


III

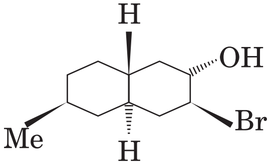
4. Give structures, including stereochemistry, of compounds A and B in the following sequence of reactions:



5. Among the following two isomeric bromohydrins I reacts with alkali to form an epoxide but II does not. Explain.

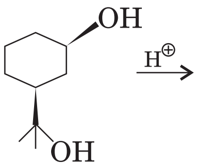


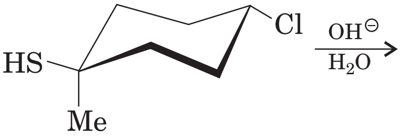
I



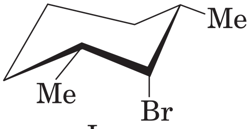
II

6. Predict the products of the following reactions and account for their formations:

(a) 

(b) 

7. Out of the three diastereoisomeric 2-bromo-1,3-dimethylcyclohexane, only one cannot undergo E2 dehydrobromination and the only product obtained from the other two is 1,3-dimethylcyclohexene. Identify these diastereoisomers and account for these observations.



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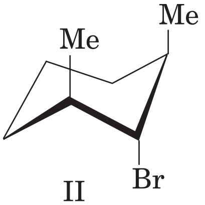

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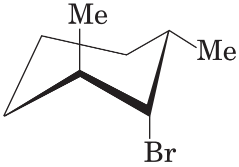
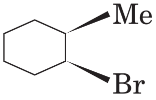


III

8. Arrange the following compounds in order of decreasing E2 reaction rate and explain the order:



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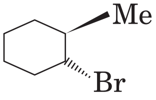

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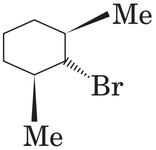
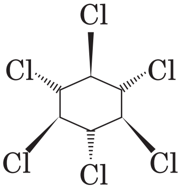


III

$$\left[\textbf{Hint:}\frac{\text{I, II, III}}{\text{E2 rate decreases}}\right]$$

9. Which one of the following hexachlorocyclohexanes is the least reactive in an E2 reaction and why?



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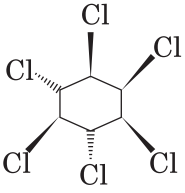

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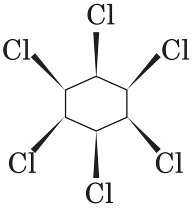
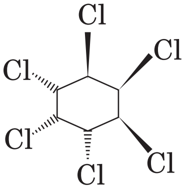


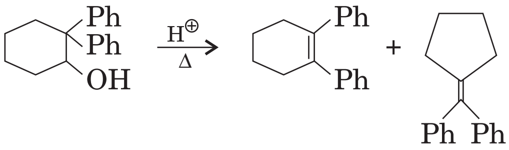
III



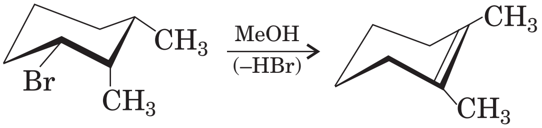
IV

10. Suggest a mechanism for each of the following reactions:

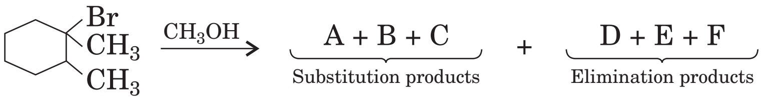
(a)



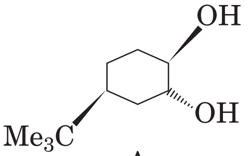
(b)



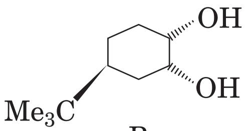
11. When the following alkyl bromide is treated with methanol, three substitution products and three elimination products are obtained. Account for the formations of these products.



12. Which one of the following diols (A or B) cannot be cleaved by periodic acid (HIO_4) and why?



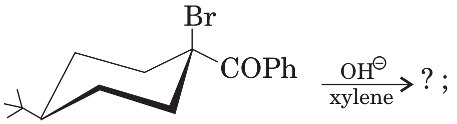
A

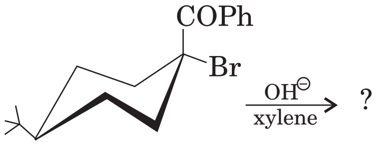


B

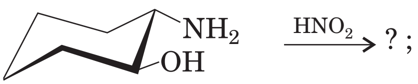
13. Predict the product and suggest a mechanism for each of the following reactions:

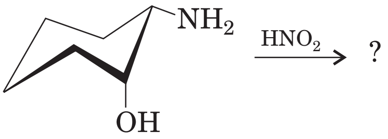
(a)



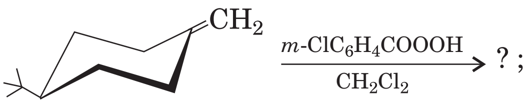


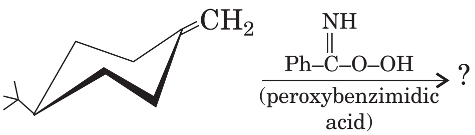
(b)





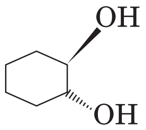
(c)



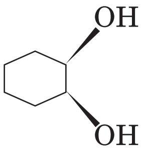


14. The *cis*- and the *trans*-isomer of cyclohexane-1,2-diol are treated with: (i) 1 mole of Ac_2O; (ii) a second mole of Ac_2O. Are the rates of the first and second acetylation reactions the same or different? Give your reasoning.

15. Which one of the following glycols cannot be cleaved by HIO_4? Give your reasoning.



I



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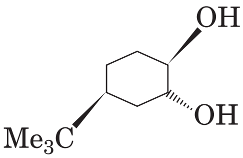
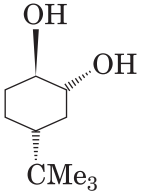
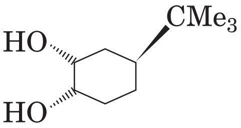


III



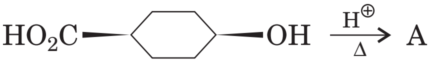
IV



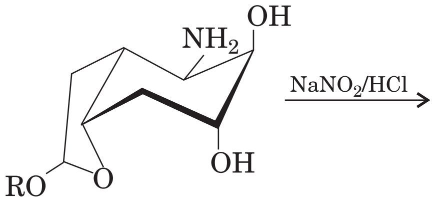
V

[**Hint:** Compound III; a cyclic intermediate cannot be formed with the glycol having two–OH groups axially oriented.]

16. Identify the compound A:

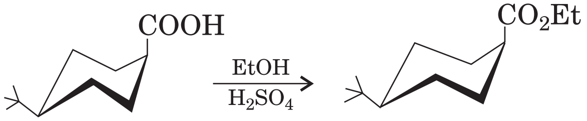


17. Predict the product of the following reaction:

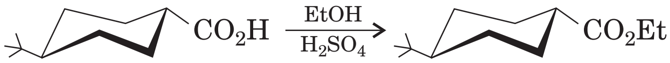


18. Which reaction is faster and why?

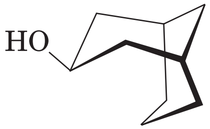
(a)



(b)

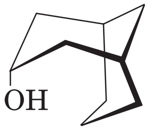


19. Which compound will be more readily oxidized by chromic acid?



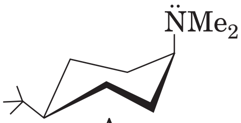
I

or



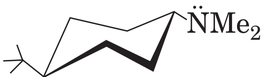
II

20. Which isomer will be converted to a quaternary salt more rapidly?



A

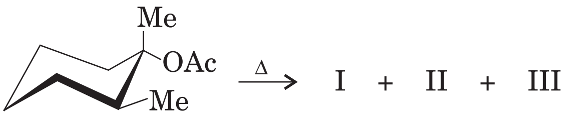
or



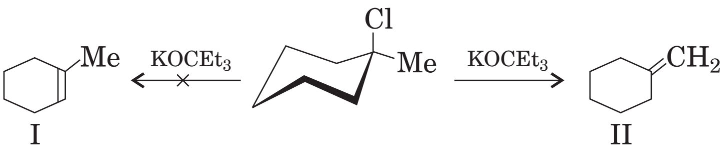
B

[**Hint:** B is more reactive because quaternary salt formation from A will increase *syn-axial* interaction.]

21. Predict the products of the following reaction and give mechanistic explanation for their formation:



22. Explain the following observations:

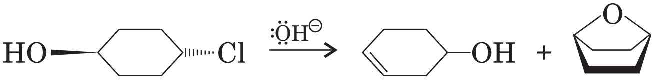


I

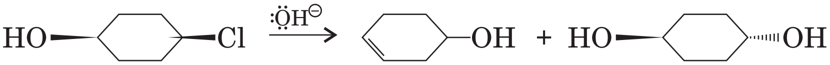
II

[**Hint:** Since the axial β-hydrogens are in a crowded environment, therefore, the bulky base, $\overset{\ominus}{\ddot{C}}Et_3$, cannot abstract them to give I.]

23. Give a curved-arrow mechanism for the formation of each product:

(a) 

trans-4-Chlorocyclohexanol

(b) 

cis-4-Chlorocyclohexanol

References

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2. Bassendale, A. *The Third Dimension of Organic Chemistry*; Wiley: New York, 1984.
3. Eliel, E. L. et al. *Conformational Analysis*; Wiley—inter-science: New York, 1965.
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5. Nasipuri, D. *Stereochemistry of Organic Compounds* (*Principles and Applications*); 3rd ed.; New Age International Publishers.

Pericyclic Reactions

8

Chapter Outline

Introduction

8.1 Construction of Molecular Orbitals
- 8.1.1 π-Molecular Orbitals of Ethylene, 1,3-Butadiene and 1,3,5-Hexatriene.
- 8.1.2 Molecular Orbitals of Conjugated Ions and Radicals
- 8.1.3 Frontier Molecular Orbitals (FMO)
- 8.1.4 Thermal and Photochemical Pericyclic Reactions

8.2 Electrocyclic Reactions
- 8.2.1 FMO Approach for Electrocyclic Reactions
- 8.2.2 Woodward and Hoffmann Selection Rules for Electrocyclic Reactions

8.3 Cycloaddition Reactions
- 8.3.1 FMO Theory of Cycloaddition Reactions
- 8.3.2 Woodward and Hoffmann Selection Rules for Cycloaddition Reactions
- 8.3.3 Diels–Alder Reactions

8.4 Sigmatropic Reactions (Rearrangements)
- 8.4.1 FMO Rationalization for the Sigmatropic Shift of Hydrogen
- 8.4.2 FMO Rationalization for the Sigmatropic Shift of Carbon
- 8.4.3 Woodward–Hoffmann Selection Rules for [i, j] Sigmatropic Shift (where $i = 1$)
- 8.4.4 FMO Rationalization for [3,3] Sigmatropic Rearrangements
- 8.4.5 Cope Rearrangements
- 8.4.6 Claisen Rearrangements

INTRODUCTION

There are a large number of chemical reactions which proceed neither through ionic nor through radical pathway and are insensitive to the presence of polar solvents and catalysts. Such reactions following a concerted mechanism involving simultaneous bond breaking and bond making and proceeding *via* a cyclic transition state which is associated with cyclic array of interacting orbitals of atoms are called *pericyclic reactions*. These reactions are classified as (i) *Electrocyclic reactions*, (ii) *Cycloaddition reactions* and (iii) *Sigmatropic reactions* (rearrangements). Pericyclic reactions are initiated either thermally or photochemically. Therefore, the energy of activation for pericyclic reactions is supplied by heat or by UV light. Since these reactions are highly stereospecific and reversible in nature, they draw special interest to the synthetic organic chemists. For the same substrate, thermal and photochemical reactions give the product with opposite stereochemistry. Pericyclic reactions are believed to be orbital controlled. In a pericyclic reaction, a set of molecular orbitals (MOs) of the reactant(s) are transformed into the corresponding set of molecular orbitals of the product(s) through a cyclic concerted process.

There are three different approaches to rationalize these pericyclic reactions:

1. *R.B. Woodward and R. Hoffmann* have proposed explanation based upon the symmetry of the molecular orbitals of the reactants and products. The theory proposed is known as *Conservation of Orbital Symmetry* (orbital symmetry correlation method).
2. *K. Fukuii* explained these reactions on the basis of frontier molecular orbitals. The theory proposed is known as *Frontier Molecular Orbital* (*FMO*) approach.
3. *Hückel-Möbius transition state* (aromatic and antiaromatic TS) *theory* developed by *H. Zimmerman* and *M.J.S. Dewar*.

8.1 CONSTRUCTION OF MOLECULAR ORBITALS

8.1.1 π-Molecular Orbitals of Ethylene, 1,3-Butadiene and 1,3,5-Hexatriene

1. Molecular orbitals of ethylene Two p atomic orbitals combine to form two π-molecular orbitals of ethylene that differ in energy. Formation of bonding and antibonding MOs on combination of two p-orbitals are shown in Fig. 8.1. The bonding MO π and the antibonding MO π^* are designated as ψ_1 and ψ_2^*, respectively. In the ground state of ethylene, ψ_1 is called HOMO (Highest Occupied Molecular Orbital) as it is occupied with two electrons, while ψ_2^* is called LUMO (Lowest Unoccupied Molecular Orbital) as it is vacant. The terms highest and lowest are used to indicate the energy levels of the two orbitals. Each p-orbital consists of two lobes, with two opposite phases of wave function indicated with the plus and minus signs. In the bonding molecular orbital (BMO) of ethylene, there is overlap of lobes having similar phase sign. This is what is called the *constructive overlap*. In the antibonding molecular orbital (ABMO), there is overlap of lobes having opposite phase sign. This is what is called *destructive overlap*. In bonding orbital, the electron charge is concentrated in the region between the two nuclei, thereby resulting in increased repulsion between the two nuclei. On photochemical excitation of the molecule, a C═C π-bond can be broken as diradical and then one of the π-electrons can be promoted to π^* by absorbing energy from light of certain wavelengths. However, the spin of the electron does not change. This refers to ethylene in excited state when the MOs, π and π^* are redesignated as SOMO-1 (First Singly Occupied Molecular Orbital) and SOMO-2 (Second Singly Occupied Molecular Orbital) or HOMO (Highest Occupied Molecular Orbital), respectively.

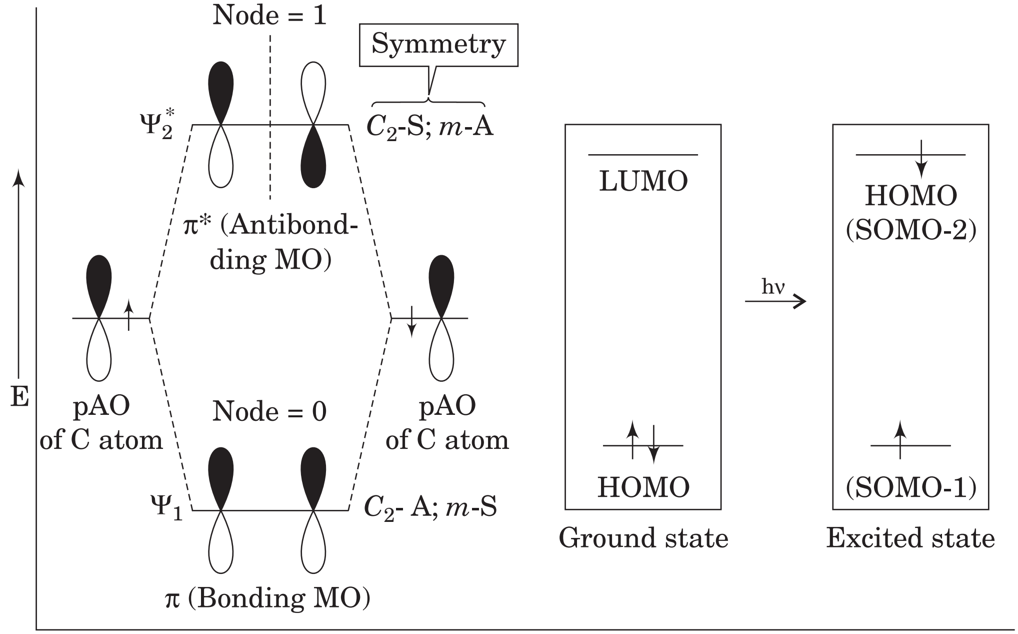


Fig. 8.1 π **Molecular orbitals of ethylene**

A *node* is a plane at which any wave, including an electron wave (orbital), is zero, i.e. when an electron is in a given MO, there is zero *probability of finding the electron*, or zero *electron density*, at the node. The bonding molecular orbital of lowest energy, ψ_1, has no new nodes (it has already a node in the plane of the molecule, which is a node of the component 2p-orbitals. ψ_2^* has one new node. Each molecular orbital of increasing higher energy has one additional node.

2. Molecular orbitals of 1,3-butadiene In 1,3-butadiene, with four component p-orbitals, there are four molecular orbitals for π electrons. We can get the four new MOs in a number of equivalent ways. One of the ways to obtain four new molecular orbitals is by linear combination of two molecular orbitals of ethylene. This is shown in Fig. 8.2. These four new orbitals are indicated as ψ_1, ψ_2, ψ_3^* and ψ_4^*. The lowest energy MO, ψ_1 has no new nodes and the bonding is best here. The next higher MO, ψ_2 has one new node between C-2 and C-3. Likewise ψ_3 has two new nodes and ψ_4 has three. Therefore, the energy of MOs gradually increases from ψ_1 to ψ_4^*. These four MOs may also be classified by S (symmetric) and A (antisymmetric) with respect to a plane passing through the middle of C-2—C-3. Of the four electrons, two are occupied in ψ_1 and two are in ψ_2 in the ground-state of butadiene. In this case, ψ_2 is HOMO and ψ_3^* is LUMO. The ground state electronic configuration of 1,3-butadiene is $\psi_1^2\psi_2^2\psi_3^*\psi_4^*$. When butadiene is irradiated photochemically by absorption of a photon of UV light, one electron from ψ_2 is promoted to ψ_3^* and the electronic configuration of the excited state becomes $\psi_1^2\psi_2^1\psi_3^{*1}\psi_4^*$. In this case,

ψ_2 is LUMO and ψ_3^* is HOMO. The singly occupied ψ_2 and ψ_3^* may also be designated as SOMO-1 and SOMO-2 respectively. Due to presence of single electron in ψ_2 as well as in the antibonding MO, ψ_3^*, the molecule in the excited state is less stable than when it is in the ground state.

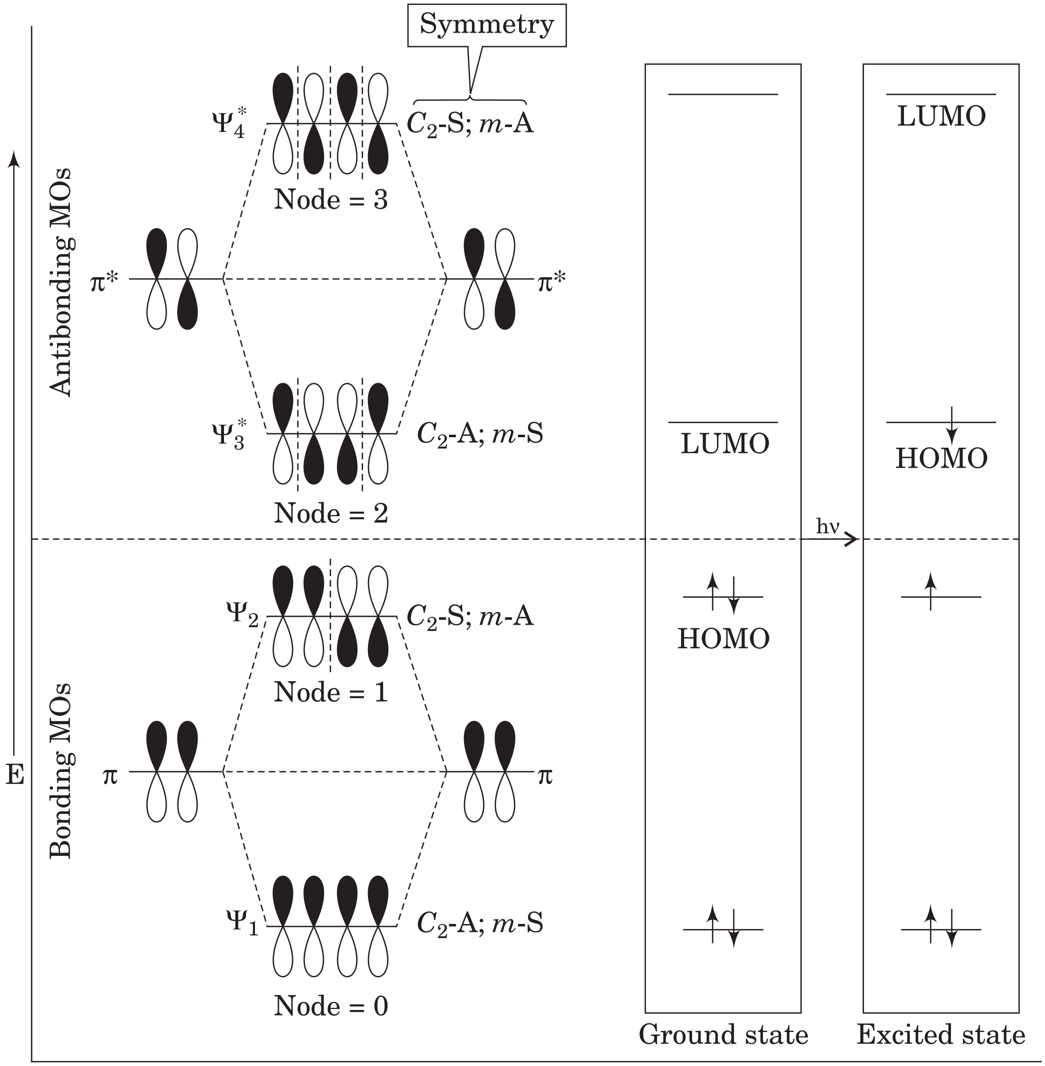


Fig. 8.2 π Molecular orbitals of 1,3-butadiene

3. Molecular orbitals of 1,3,5-hexatriene Since 1,3,5-hexatriene is a conjugated system of three C=C bonds, it involves a total of six molecular orbitals which are designated as ψ_1, ψ_2, ψ_3, ψ_4^*, ψ_5^* and ψ_6^*. The first three MOs ψ_1 to ψ_3 are filled in the ground state and are of lower energy and bonding. The remaining three ψ_4^* to ψ_6^* are empty and of higher energy and antibonding. On photochemical irradiation of the triene molecule one of the electron is promoted from ψ_3 to ψ_4^*. Therefore, the electronic configuration of the molecule in the excited state is $\psi_1^2\psi_2^2\psi_3^1\psi_4^{*1}\psi_5^*\psi_6^*$. The π-molecular orbitals of 1,3,5-hexatriene is shown in Fig. 8.3.

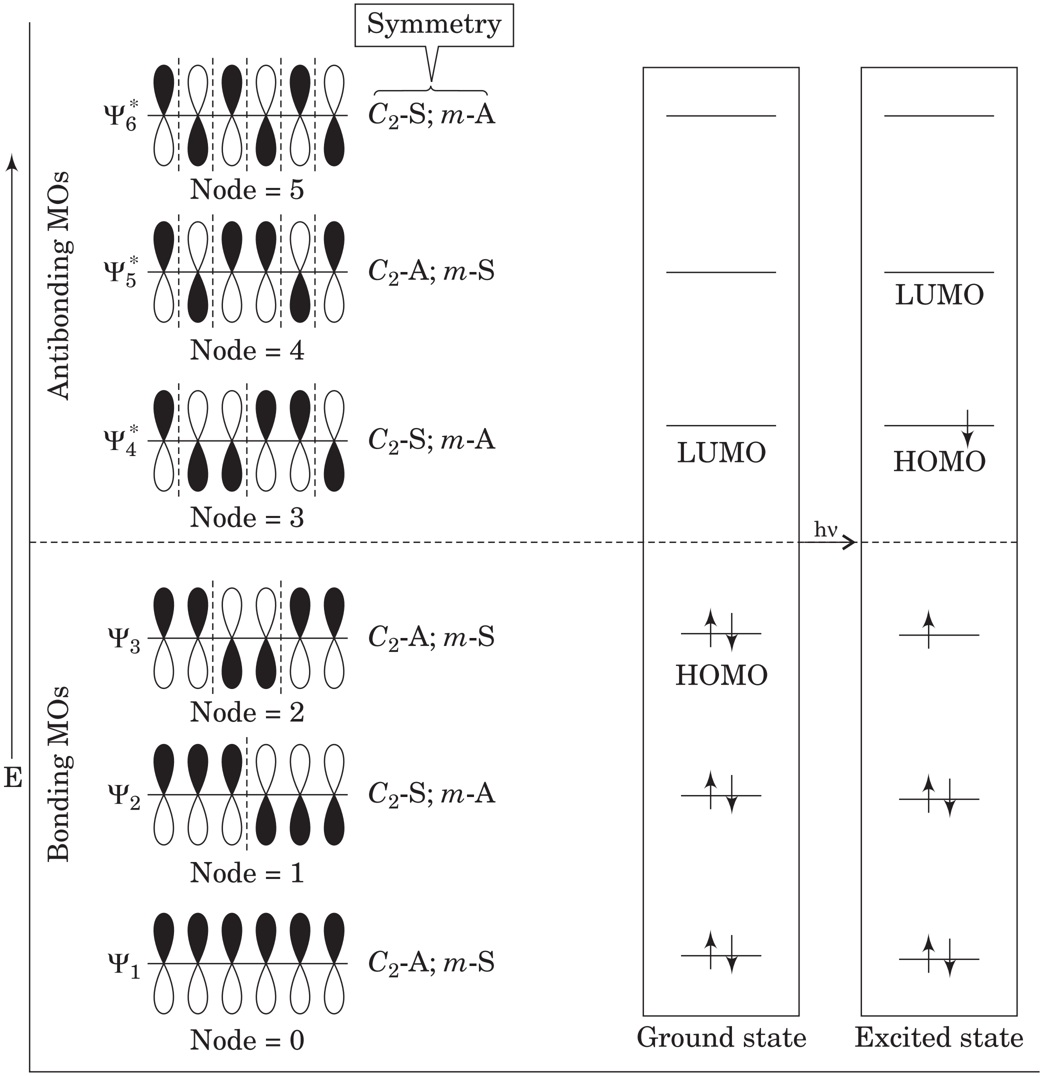
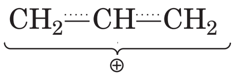


Fig. 8.3 π Molecular orbitals of 1,3,5-hexatriene

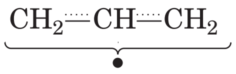
8.1.2 Molecular Orbitals of Conjugated Ions and Radicals

1. Molecular orbitals of allyl system There are three types of allyl system: cation, radical and anion. Regardless of the number of π electrons, there are three component p-orbitals, one on each carbon, and they give rise to three molecular orbitals ψ_1 ψ_2 and ψ_3.



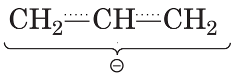
$\underbrace{CH_2\overset{\cdots}{—}CH\overset{\cdots}{—}CH_2}_{\oplus}$

Allyl cation
(a 2π electron system)



$\underbrace{CH_2\overset{\cdots}{—}CH\overset{\cdots}{—}CH_2}_{\bullet}$

Allyl radical
(a 3π electron system)



$\underbrace{CH_2\overset{\cdots}{—}CH\overset{\cdots}{—}CH_2}_{\ominus}$

Allyl anion
(a 4π electron system)

As shown in the Fig. 8.4, ψ_1 is bonding and ψ_3 is antibonding. The MO ψ_2 encompasses only the end carbons (there is a node at the middle carbon) and it has the same energy as on isolated p-orbital. Therefore, it is non-bonding. ψ_1 has no additional nodes and ψ_3 has two additional nodes (between C-1—C-2 and C-2—C-3). Allyl cation has π electrons only in the bonding orbital. Allyl radical has one electron in the non-bonding orbital as well, and allyl anion has two electrons in the non-bonding orbital.

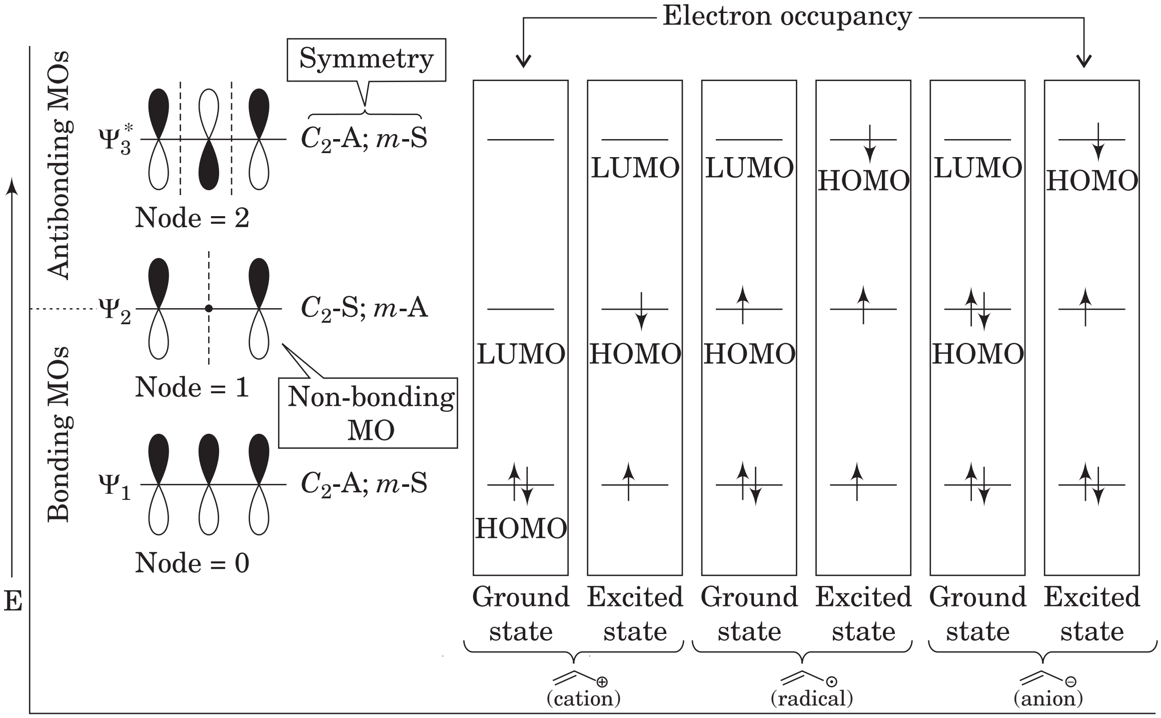
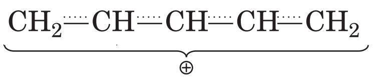


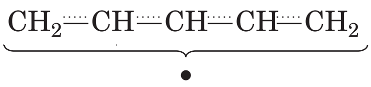
Fig. 8.4 π-Molecular orbitals of allyl system

2. Molecular orbitals in pentadienyl system Although the total number of MOs is five, the situation in this case is very similar to that of the allyl system. The MOs are shown in the following figure (Fig. 8.5).



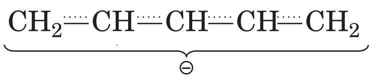
$\underbrace{CH_2\overset{\cdots}{—}CH\overset{\cdots}{—}CH\overset{\cdots}{—}CH\overset{\cdots}{—}CH_2}_{\oplus}$

Pentadienyl cation
(a 4π electron system)



$\underbrace{CH_2\overset{\cdots}{—}CH\overset{\cdots}{—}CH\overset{\cdots}{—}CH\overset{\cdots}{—}CH_2}_{\bullet}$

Pentadienyl radical
(a 5π electron system)



$\underbrace{CH_2\overset{\cdots}{—}CH\overset{\cdots}{—}CH\overset{\cdots}{—}CH\overset{\cdots}{—}CH_2}_{\ominus}$

Pentadienyl anion
(a 6π electron system)

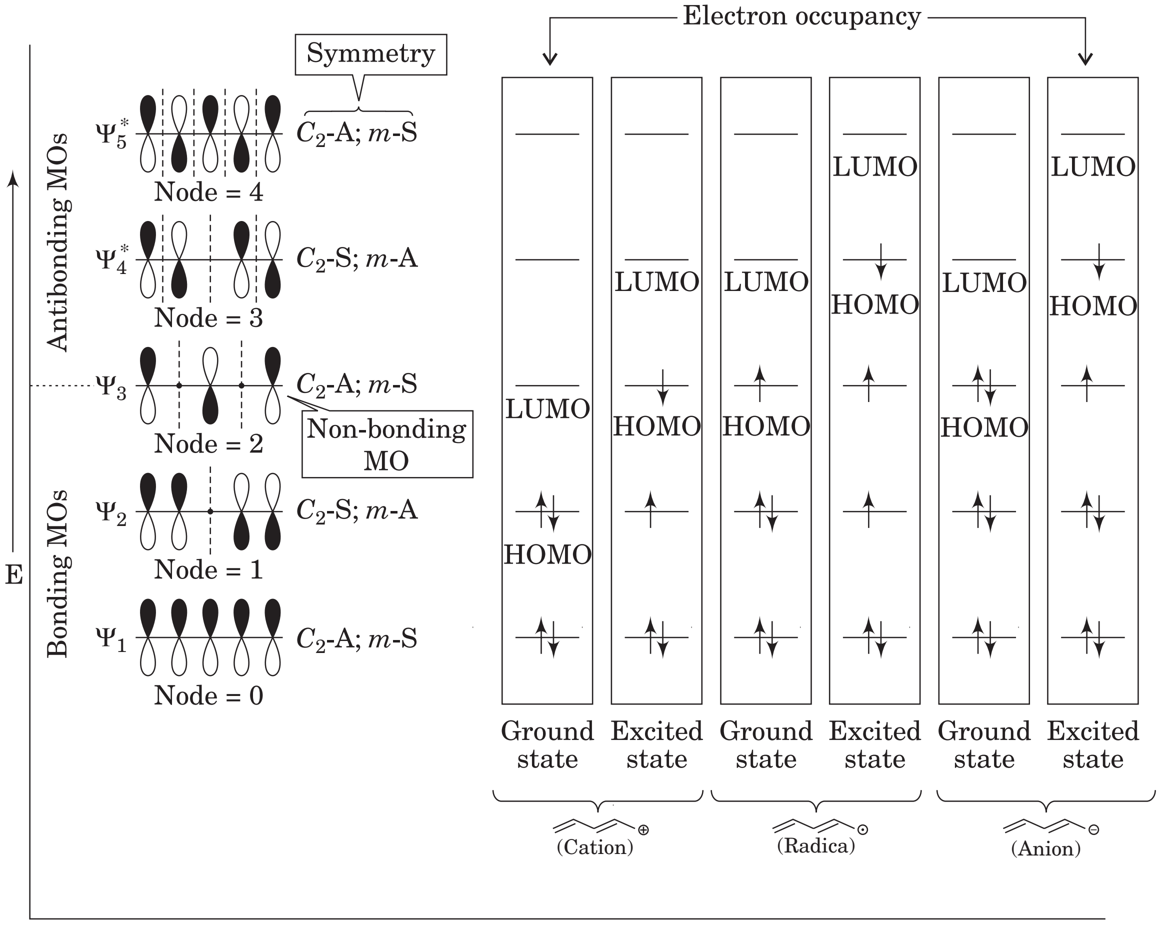


Fig. 8.5 π-Molecular orbitals of pentadienyl system

8.1.3 Frontier Molecular Orbitals (FMO)

Pericyclic reactions proceed through cyclic transition states. Therefore, there occurs a high degree of ordering, i.e., loss of entropy ($\Delta S^{\ddagger}$ = –ve) in the T.S. which may not be favourable for a reaction to take place smoothly. Hence, to overcome the loss of entropy ($\Delta S^{\ddagger}$), the enthalpy ($\Delta H^{\ddagger}$) of formation of T.S., must be high enough, i.e., it must be sufficiently negative, so that $\Delta G^{\ddagger}$ term becomes negative ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$) to make the reaction feasible. A high negative value of $\Delta H^{\ddagger}$ requires a high degree of bonding through a very good overlap of MOs in the transition state. It, thus, follows that the success of a pericyclic reaction depends on the extent of orbital overlapping in the T.S.

A good orbital overlapping between two molecules or two parts of a single molecule, say, I and II, depends on the following factors: (i) the type of orbitals (2*p*-2*p*, 2*p*-3*p*, 2*p*-4*p*, etc.) involved in overlapping, (ii) the electron content of the orbitals, i.e., whether they are filled or vacant or one is vacant and another is filled, (iii) the energy of the overlapping orbitals, (iv) the stereochemistry of the orbitals involved and (v) the phase sign of the overlapping orbitals. When a filled orbital of one component interacts with a vacant orbital of another component of comparable energy and same phase sign (i.e., when the combining orbitals have the same symmetry property), a perfect overlap of molecular orbitals takes place. This can be verified from Fig. 8.6 by considering all sorts of orbital interactions possible when the component X approaches the component Y. The MOs in the centre in each of the figures (a and b) are the approximation of two of the orbitals in the T.S. The best bonding interaction takes place when HOMO of X overlaps with LUMO of Y (Fig. 8.6a) and this is because there occurs largest drop of energy on bonding. The energy drop is much less when HOMO of X overlaps with the HUMO (Highest Unoccupied Molecular Orbital) of Y (Fig. 8.6b) and therefore, this interaction is less effective. If the HOMO of X is considered to overlap with HOMO of Y, both bonding and antibonding molecular orbitals have two electrons in each. This corresponds to the bond order $= \frac{1}{2} \times (\mathrm{N_b} - \mathrm{N_a}) = \frac{1}{2} \times (2 - 2) = 0$. This indicates that there is no bonding at all. The interaction of other occupied and unoccupied orbitals also causes reduction of T.S. energy but the amount is much smaller than that of the HOMO–LUMO interaction. The question of bonding by the overlap of two unoccupied orbitals does not arise because there is no electron in those orbitals. Therefore, it becomes clear that HOMO and LUMO lead to successful bonding on their overlap. These are sometimes collectively called *Frontier Molecular Orbitals* (FMO) because they are the molecular orbitals at the energy extremes: the HOMO is the occupied molecular orbital of highest energy, and the LUMO is the unoccupied molecular orbital of lowest energy. The analysis of pericyclic reactions focuses heavily on the symmetries (m and C_2) of frontier orbitals. The importance of HOMO and LUMO in determining the course of a concerted reaction may also be considered as follows. The electrons in the HOMO of a molecule are like the outer shell electrons of an atom. They can be removed with least expenditure of energy because they are already in the highest energy level than any of the other electrons in the molecule. The LUMO (Lowest Unoccupied Molecular Orbital) of a molecule is the orbital to which electrons can be transferred with the least expenditure of energy. The higher the energy of HOMO of a molecule, the more easily the electrons can be removed from it. On the other hand, the lower the energy of LUMO of the molecule, the more easily the electrons can be transferred into it. Hence, the interaction between a molecule with a HOMO of higher energy and a molecule with a LUMO of lower energy is particularly strong.

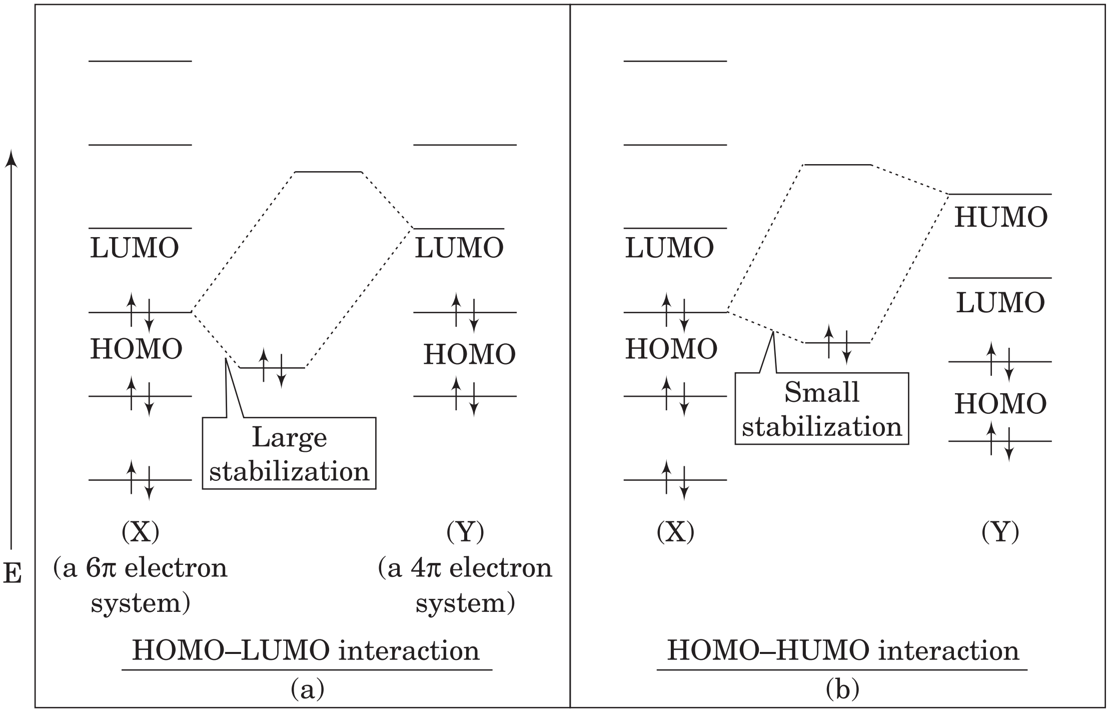
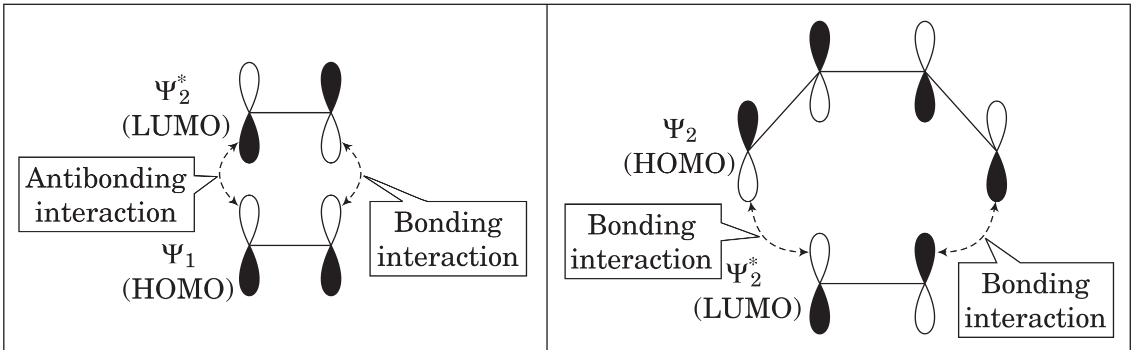


Fig. 8.6 Energy diagram for the interaction of two MOs

Application of FMO theory The FMO theory states that a pericyclic reaction reaction will be allowed if there occurs a favourable interaction (i.e., in-phase interaction) between HOMO and LUMO and will be forbidden if there occurs an unfavourable interaction (out-of-phase interaction) between them. This method is very useful in deciding whether the transition state of a pericyclic reaction will be stabilized as the reaction begins to take place. For example, the thermal $[\pi^2 + \pi^2]$ cycloaddition reaction between two ethylene molecules does not occur at all, while the $[\pi^4 + \pi^2]$ cycloaddition reaction between 1,3-butadiene and ethylene occurs smoothly, i.e., the reaction is thermally allowed. If we consider the frontier orbital interactions for both the reactions, we see that in the [2 + 2] cycloaddition reaction, there is an antibonding (out of-phase) interaction at one end and hence this causes no net stabilization of the T.S. But in [4 + 2] cycloaddition reaction, there occurs bonding (in-phase) interaction at both ends and hence this causes net stabilization of the T.S. In fact, the symmetry is conserved during the course of [4 + 2] cycloaddition reaction and the process is known as *symmetry allowed* process and the symmetry is not conserved during the course of [2 + 2] cycloaddition reaction and the process is known as *symmetry forbidden* process. The energy of the T.S. of symmetry-allowed process is always lower than the symmetry forbidden process.



[2 + 2] cycloaddition
Thermally forbidden

[4 + 2] cycloaddition
Thermally allowed

8.1.4 Thermal and Photochemical Pericyclic Reactions

The normal electronic configuration of any molecule is called the *ground state*. Energy from absorbed light is used to promote an electron from the HOMO of ground-state 1,3-butadiene (ψ_2), for example, into the LUMO (ψ_3^*). A species with a promoted electron is called an excited state. Pericyclic reactions can be differentiated according to whether they are *thermal* or *photochemical*. A *thermal pericyclic reaction* is any pericyclic reaction not activated by light, i.e., such reactions occur through molecular *ground states*. A *photochemical pericyclic reaction* is any pericyclic reaction activated by light, i.e., such reactions occur through molecular *excited states*.

SOLVED PROBLEMS

1. **What is called 'Perturbation Theory'? How would you show that the energy (E) of molecular orbitals is equal to $\alpha \pm \beta$? What are the energies of ψ_1 and ψ_2^* of ethylene?**

Solution The description of molecular orbitals in terms of interacting atomic orbitals (AOs) is called 'Perturbation Theory'. When two atomic orbitals coming together perturb each other, two molecular orbitals (MOs), one with higher energy than either atomic orbital and one of lower energy, are obtained. The extent of interaction of two atomic orbitals can be described using three parameters.

(i) The *Coulomb integral*, α, which denotes the energy of the isolated atomic orbital.
(ii) The *Overlap integral*, S, which denotes a measure of the extent of the overlap between the interacting atomic orbitals.
(iii) The *resonance* or *bond integral,* β, which is related to the energy of interaction.

The energy, E, of the molecular orbitals formed from atomic orbitals A and B can be expressed in terms of these parameters as follows:

$$(\alpha_A - E)(\alpha_B - E) = (\beta - SE)^2 \tag{1}$$

If the two atomic orbitals are degenerated, $\alpha_A = \alpha_B = \alpha$, then the equation (1) becomes

$$(\alpha - E)^2 = \pm(\beta - SE)^2, \text{ or } (\alpha - E) = \pm(\beta - SE)$$

Therefore, $$E = \frac{\alpha + \beta}{1 + S} \quad \text{or} \quad E = \frac{\alpha - \beta}{1 - S} \tag{2}$$

If the overlap integral S is neglected for simplification, the energy of the molecular orbitals becomes

$$E = \alpha \pm \beta \tag{3}$$

where $(\alpha + \beta)$ represents the energy of bonding molecular orbital and $(\alpha - \beta)$ represents the energy of antibonding molecular orbital. The π-bond in ethylene can be treated in isolation as the interaction between two unhybridized p-orbitals, independent of the σ-framework, which lies in a plane perpendicular to them. Their mutual perturbation generates one bonding and one antibonding pi-molecular orbitals having energies given by the equation $E = \alpha \pm \beta$. Therefore, the energies of ψ_1 and ψ_2^* of ethylene are $\alpha + \beta$ and $\alpha - \beta$, respectively.

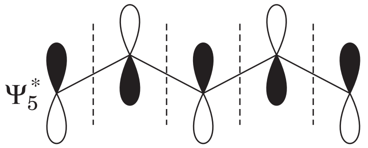
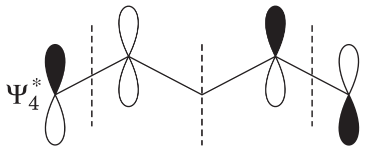
2. **Indicate the following numbers for 1,3,5-hexatriene:**
 (a) no. of interacting p-atomic orbitals, (b) no. of molecular orbitals formed, (c) no. of BMO (Bonding Molecular Orbital), (d) no. of ABMO (Antibonding Molecular Orbital), (e) no. of NBMO (Non-bonding Molecular Orbital) and (f) no. of π electrons.

Solution

(a) No. of interacting p-atomic orbital = 6, (b) No. of molecular orbitals formed = 6, (c) No. of BMO = 3, (d) No. of ABMO. = 3, (e) No. of NBMO = 0, and (f) No. of π electrons = 6.

3. **Draw the LUMO of pentadienyl anion and cation at the excited state indicating nodes and symmetry.**

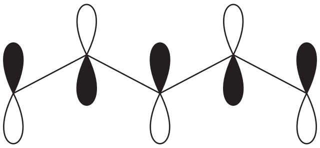
Solution

MOs at the excited state	Node	C_2	m
 LUMO of pentadienyl anion	4	A	S
 LUMO of pentadienyl cation	3	S	A

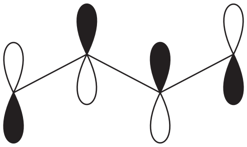
A = Antisymmetric, S = Symmetric

4. Indicate the following MOs as bonding, antibonding or non-bonding MO:

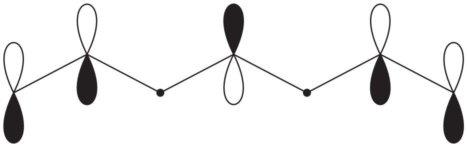
(a)



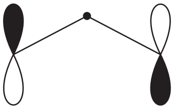
(b)



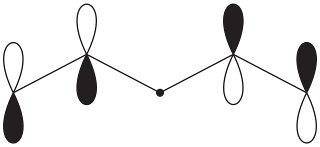
(c)



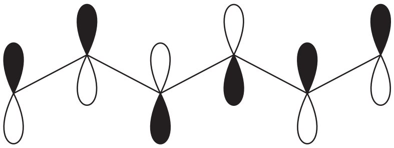
(d)



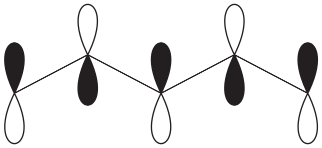
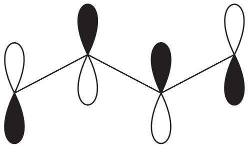
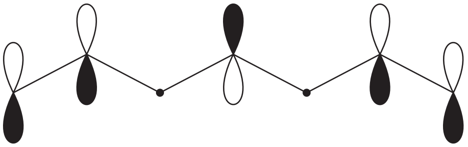
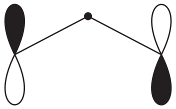
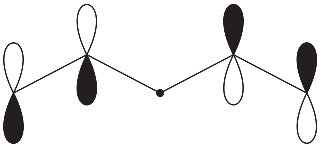
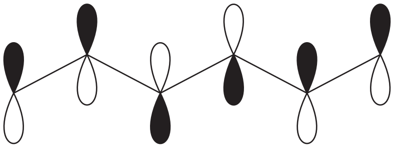
(e)



(f)



Solution

MO diagram	No. of bonding interaction	Type of MO
(a) 	(–1) + (–1) + (–1) + (–1) = –4	Antibonding MO
(b) 	(–1) + 1 + (–1) = –1	Antibonding MO
(c) 	+1 + 0 + 0 + 0 + 0 + 1 = +2	Bonding MO
(d) 	0 + 0 = 0	Non-bonding MO
(e) 	+1 + 0 + 0 + 1 = +2	Bonding MO
(f) 	+1 + (–1) + 1 + (–1) + 1 = +1	Bonding MO

5. Write down the answers of the following questions for 1,3,5-hexatriene ($CH_2{=}CH{-}CH{=}CH{-}CH{=}CH_2$) containing six carbon atoms.

(a) How many π-molecular orbitals are there in this molecule?

(b) Classify the molecular orbitals as symmetric or antisymmetric about a reference plane passing through the centre of the molecule and perpendicular to the plane of the molecule.

(c) Indicate the bonding and antibonding molecular orbitals.

(d) Indicate the FMOs.

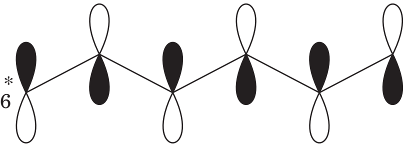
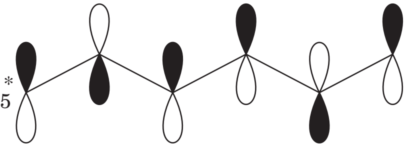
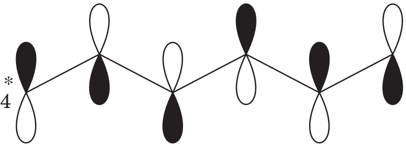
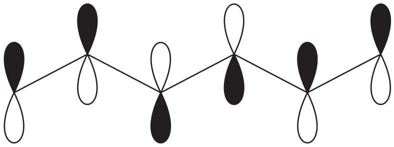
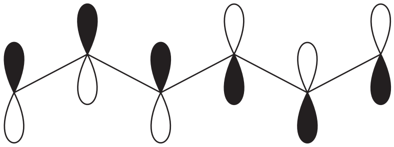
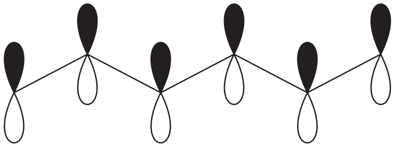
(e) Within the excited state HOMO, is the phase at the terminal carbons the same or different?

(f) Within the excited state LUMO, is the phase at the terminal carbons the same or different?

Solution

(a) Since there are six p-atomic orbitals in the molecule, the number of π-molecular orbital is six.

(b)

MOs	*m*
Ψ_6^* 	A
Ψ_5^* 	S
Ψ_4^* 	A
Ψ_3 	S
Ψ_2 	A
Ψ_1 	S

(c) ψ, ψ_2 and ψ_3 are bonding MOs and ψ_4^*, ψ_5^* and ψ_6^* are antibonding MOs.

(d) ψ_3 is HOMO and ψ_4^* is LUMO.

(e) ψ_4^* in the excited state HOMO and within it the phase at the terminal carbons is different.

(f) ψ_5^* is the excited state LUMO and within it the phase at the terminal carbons is the same.

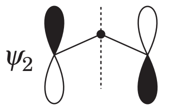
6. (a) What are the two important differences between the MOs of conjugated ions (and redicals) having an odd number of carbon atoms and those of conjugated alkenes?

(b) How would you explain that the charge in the allyl anion resides only on the terminal carbons, a point deduced from resonance arguments?

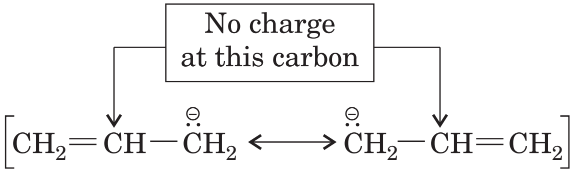
Solution

(a) The two important differences between the MOs of conjugated ions (and radicals) having an odd number of C-atoms and those of conjugated alkenes are: (i) in each ion or radical, one MO is neither bonding nor antibonding, but has the same energy as the isolated 2*p*-orbitals; this MO is called a **non-bonding molecular orbital**. The non-bonding MO in an allyl system is ψ_2. The remaining orbitals are either bonding or antibonding, and the number of each type is the same; (ii) in some of the MOs, nodes pass through carbon atoms. For example in the allyl system, there is a node on the middle carbon of ψ_2.

(b) In allyl anion, there is a node on the middle carbon of ψ_2. This means that electrons in ψ_2 have no electron density on the middle carbon. Because of this, the charge in the allyl anion resides only on the terminal carbons, a point deduced from the resonance structures of allyl anion.



Allyl anion



$$\left[CH_2{=}CH{-}\overset{\ominus}{\ddot{C}}H_2 \longleftrightarrow \overset{\ominus}{\ddot{C}}H_2{-}CH{=}CH_2\right]$$

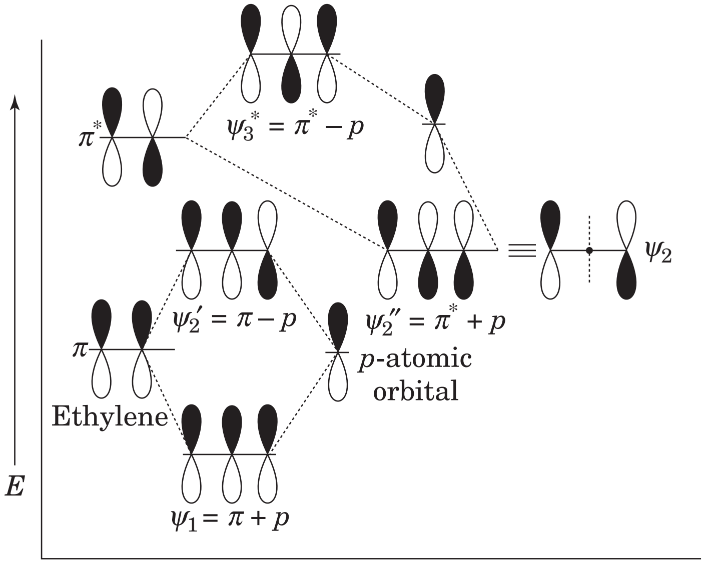
Resonance structures of allyl anion

7. What do you mean by symmetry-allowed and symmetry-forbidden reactions?

Solution In the case of FMO approach to a pericyclic reaction, when the terminal orbitals of HOMO and LUMO overlap in the same phase leading to bonding interaction, then it is called a symmetry-allowed reaction but when the HOMO–LUMO overlap is not a bonding interaction, then it is called a symmetry forbidden reaction.

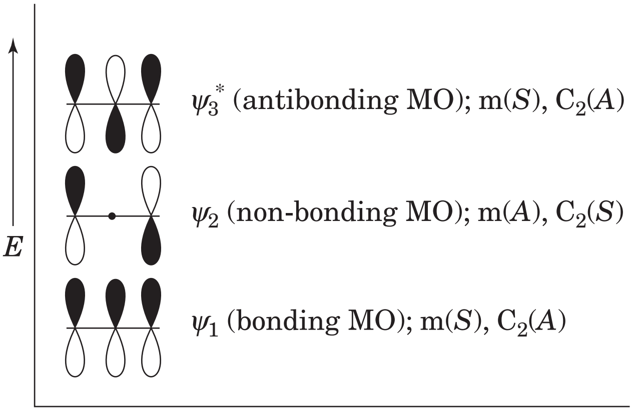
8. Draw the molecular orbitals of allyl system by the use of the linear combination of molecular orbitals of one ethylene molecule and one *p*-atomic orbital.

Solution Since in an allyl system linear combination takes place between one ethylene MO and one p-orbital, we need to look at the results of the $\pi \pm p$ and $\pi^* \pm p$ interactions.



Construction of MOs of allyl system

The ethylene bonding orbital, π gives linear combination with p-atomic orbital in a bonding way and moves down in energy to give ψ_1, whereas it gives the linear combination in an antibonding way to move the p-orbital up in energy ($\psi_2' = \pi - p$). The ethylene antibonding orbital (π^*) gives linear combination with p-orbital in a bonding way to push the p-orbital down in energy ($\psi_2'' = \pi^* + p$), whereas it gives the linear combination an antibonding way to push p-orbital up in energy to give ψ_3^*. The net result in the energy change ($\pi - p$) and $\pi^* - p$) interactions is zero. Under this situation a nodal plane passes through the central carbon of the chain. This means that electrons in ψ_2 have no electron density on the central carbon. Thus, ψ_2 must be a non-bonding molecular orbital. Thus, the molecular orbitals of the allyl system can be represented as follows:


ψ_3^* (antibonding MO); m(S), C_2(A)
ψ_2 (non-bonding MO); m(A), C_2(S)
E
ψ_1 (bonding MO); m(S), C_2(A)

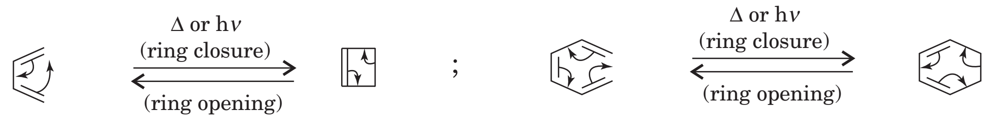
π-Molecular orbitals of allyl system

STUDY PROBLEMS

1. What is meant by ‘pericyclic reactions’? Give classification of pericyclic reactions with examples.
2. Write down some important characteristics of pericyclic reactions.
3. What do you mean by the FMO approach for analysing pericyclic reactions? Give an example.
4. What is meant by ‘conservation of orbital symmetry’? What are the symmetry elements which control the course of a pericyclic reaction?
5. What do you mean by the terms HOMO, LUMO, HUMO, SOMO and LOMO?
6. Justify the following statements:
   (a) A reaction occurs easily if the energy gap between the interacting FMOs decreases.
   (b) Interaction between molecular orbitals of different symmetry does not provide any net stabilization to the transition state of the pericyclic reaction.
7. How would you construct the π-MO diagram of the following molecule ions?
   (a) 1,3,5,7-Octatetraene, (b) 2,4,6-Heptatrienyl cation, (c) 1,3,5-Hexatriene, (d) allyl anion.
8. Draw the π-MOs of the following species as specified:
   (a) HOMO of 1,3,5,7-octatetraene at the ground and excited states.
   (b) LUMO of pentadienyl cation at the ground and excited states.
9. Draw the π-MO ψ_6 of 1,3,5,7,9-decapentane. State whether ψ_6 is (i) symmetric or antisymmetric with respect to the reference plane passing through the centre of the molecule and perpendicular to the plane of the molecule, (ii) bonding or antibonding, and (iii) a HOMO or a LUMO.
10. (a) Which MO of 2,4,6-heptatrienyl cation is non-bonding?
    (b) Classify each MO of this cation as symmetric and anti-symmetric.
    (c) To which carbon atoms in this cation is the positive charge delocalized? Explain with both molecular-orbital and resonance arguments.
11. Explain why the unpaired electron in the allyl radical is delocalized to C-1 and C-3 but not to C-2 using molecular-orbital argument as well as resonance argument.
12. Sketch the pi molecular orbitals of the allyl system. Give the electron occupancy in allyl cation, allyl anion and allyl radical.
13. Explain why the energy of ψ_5^* of 1,3,5-hexatriene is less than that of ψ_6^*.
14. Sketch the π molecular orbitals of:
    (a) $CH_3—CH{=}CH—\overset{\oplus}{C}H—CH_3$ (b) $CH_3—CH{=}CH—\overset{\ominus}{C}H—CH_3$
15. What do you mean by the terms ‘constructive overlap’ and ‘destructive overlap’.

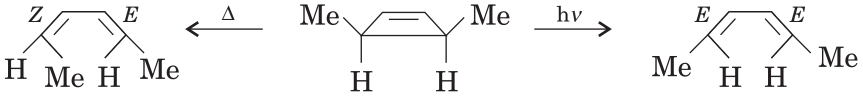
8.2 ELECTROCYCLIC REACTIONS

An electrocyclic reaction is a concerted opening of a cycloalkene or closing of a conjugated polyene through the conversion of a σ-bond to a π-bond or the reverse. These reactions are induced either thermally or photochemically. A notation with curved arrows is helpful to understand the bond cleavage and bond formation as shown below:

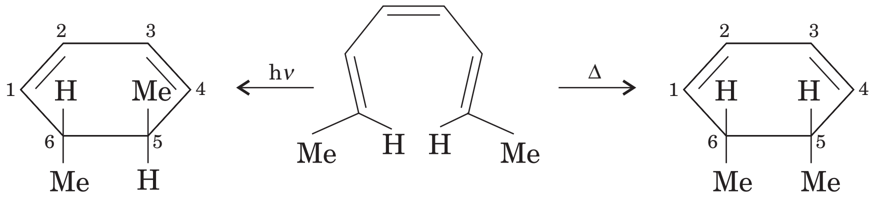


1,3-Butadiene Cyclobutene 1,3,5-Hexatriene 1,3-Cyclohexadiene

Although these reactions are reversible and the ring closure occurs with the formation of a strong σ-bond at the expense of a weaker π-bond, the ring closure of 1,3-butadiene is slower than the ring closure of 1,3,5-hexatriene and this is because the former reaction leads to the formation of a strained (thermodynamically less stable) cyclobutene system. The interesting feature of electrocyclic reactions is that the stereochemistry of the product obtained when a given compound is subjected to electrocyclic reaction thermally is just opposite to that of the product when the reaction is carried out photochemically. For example:



(2*Z*, 4*E*)-2,4-Hexadiene *cis*-3,4-Dimethyl-cyclobutene (2*E*, 4*E*)-2,4-Hexadiene



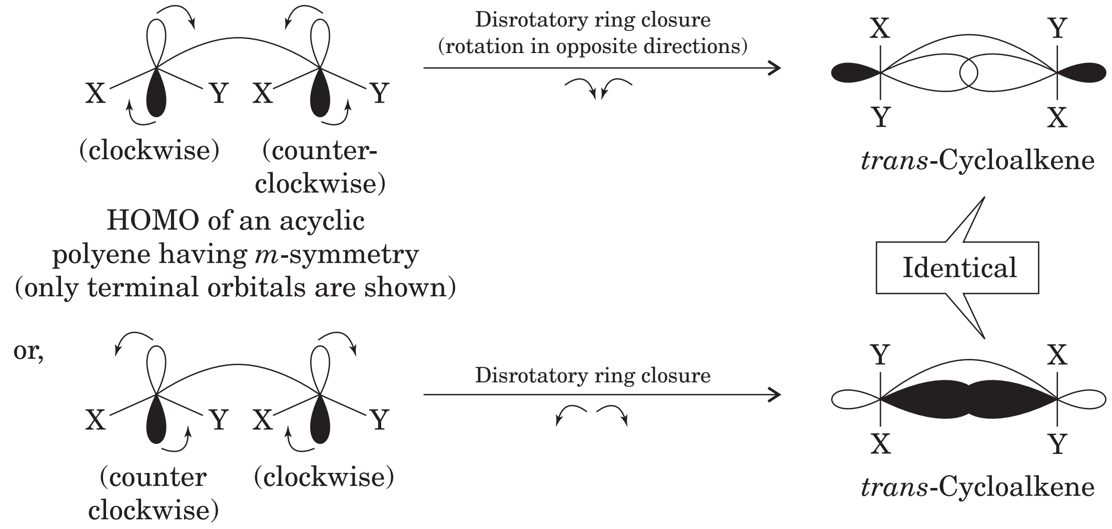
trans-5,6-Dimethyl-1,3-cyclohexadiene (2*E*, 4*Z*, 6*E*)-2,4,6-Octatriene *cis*-5,6-Dimethyl-1,3-cyclohexadiene

8.2.1 Frontier Molecular Orbital (FMO) Approach for Electrocyclic Reactions

For electrocyclic ring closure, the HOMO of the acyclic polyene is to be considered, while for electrocyclic ring opening, the HOMO of the alkene part and the LUMO of the σ bond of the cycloalkene are to be considered. During cyclization, two terminal *p*-orbitals of the HOMO of a polyene overlap in-phase in order to have bonding interaction to form a C—C σ-bond and for this, the terminal *p*-orbitals may rotate either in the same direction or in opposite directions. However, the actual direction of rotation of *p*-orbitals depends on the symmetry property of the HOMO of the concerned polyene. When the HOMO of the polyene possesses *m*-symmetry, the *p*-orbitals are to rotate in opposite directions (one clockwise and the other counterclockwise, ↶ ↷ or ↷↶) to give the product with *m*-symmetry and when the HOMO of the polyene possesses C_2-symmetry, the terminal *p*-orbitals are to rotate in the same direction (both clockwise, ↷↷ or both counterclockwise, ↶↶) to give the product with C_2-symmetry. The former mode of cyclization is said to be *disrotatory* and the latter mode of cyclization is said to be *conrotatory*.

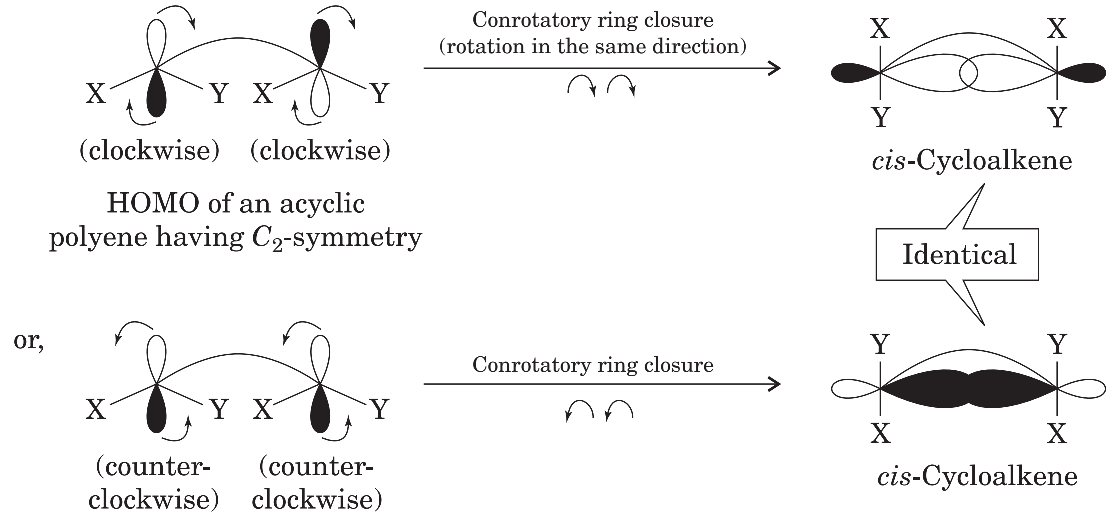
Symmetry in HOMO	Mode of rotation
m-Symmetry	Disrotatory
C_2-symmetry	Conrotatory

Disrotatory motion:



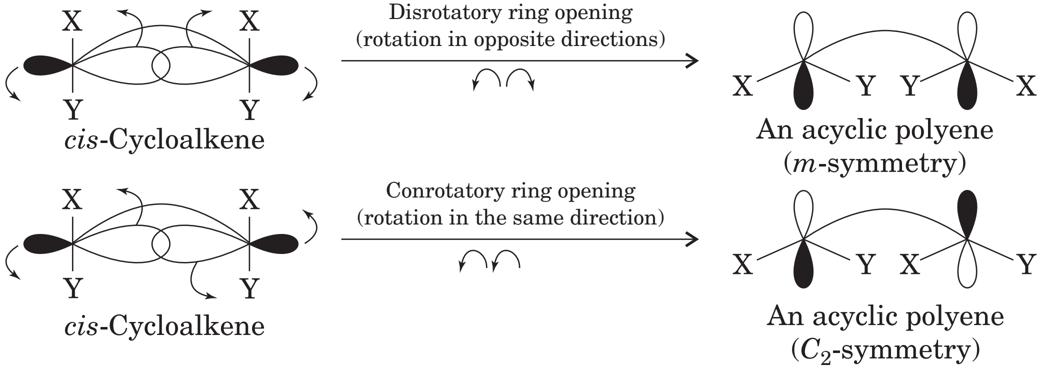
HOMO of an acyclic polyene having m-symmetry (only terminal orbitals are shown)

Conrotatory motion:



HOMO of an acyclic polyene having C_2-symmetry

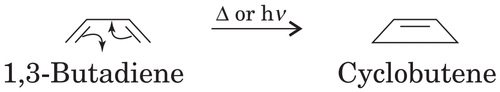
Similar situation may arise when a cycloalkene ring opens up. Direction of ring opening depends on the orbital structure of HOMO of the alkene part so that in-phase sideways overlap of the p-orbitals is maintained in the product. Alternatively, if the ground state HOMO of a polyene has C_2-symmetry (or m-symmetry) the corresponding cycloalkene ring must open in such a fashion that the σ-bond orbitals become converted to the HOMO of the product polyene having C_2-symmetry (or m-symmetry).



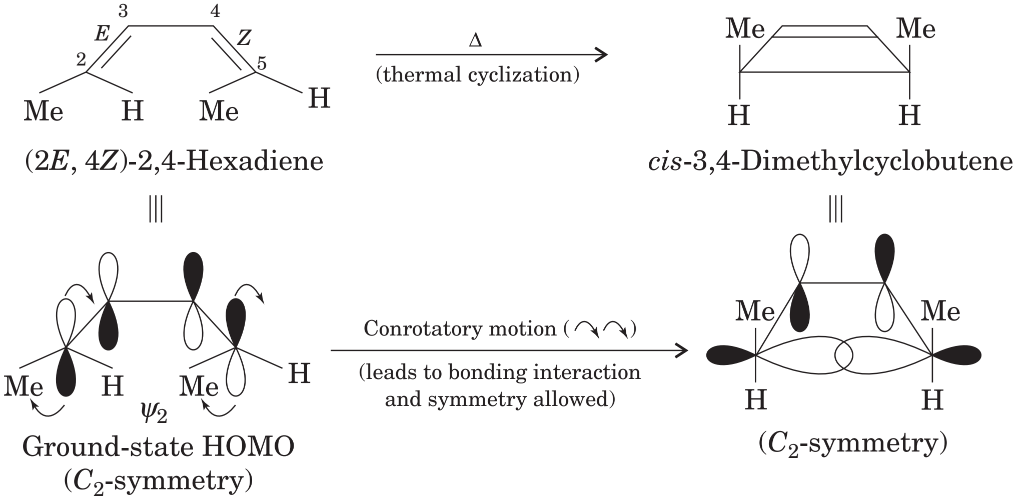
Now, we will consider the ring-closure and ring-opening reactions under thermal and photochemical conditions.

8.2.1.1 Cyclization of 4nπ Systems

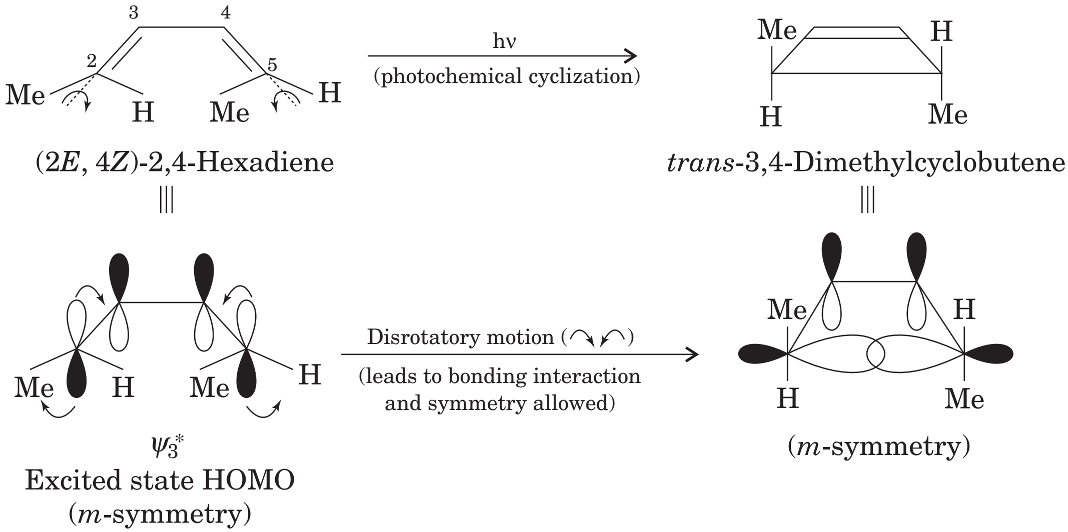
1. Electrocyclic ring-closure reactions given by 1,3-butadiene and its derivatives 1,3-Butadiene is the first member of the conjugated polyene having $4n\pi$ electrons.



Thermal cyclization of (2*E*, 4*Z*) 2,4-hexadiene For thermal cyclization, the ground state HOMO of the diene, i.e., ψ_2 is to be considered. Since this MO has C_2-symmetry, a conrotatory ring-closure gives the product. Thus, when (2*E*, 4*Z*)-2,4-hexadiene is heated, *cis*-3,4-dimethylcyclobutene is obtained and this is because conrotatory motion causes the two methyl groups to be placed on the same side of the product molecule. Disrotatory motion could not place the in-phase lobes together, i.e., it does not lead bonding-interaction and also process is symmetry forbidden, i.e., the product is C_2-asymmetric. Therefore, ring-closure does not take place by this fashion.



Photochemical Cyclization of (2*E*, 4*Z*)-2,4-hexadiene In the case of photochemical cyclization, the first excited state ψ_3^* of 1,3-butadiene is to be considered as HOMO because on photochemical irradiation one electron has been promoted from ψ_2 to ψ_3^*. Since ψ_3^* has *m*-symmetry; therefore, a disrotatory motion is required for the σ-bond formation. Thus, when (2*E*, 4*Z*)-2,4-hexadiene is subjected to photochemical cyclization, *trans*-3,4-dimethylcyclobutene is obtained and this is because disrotatory motion causes the two methyl groups to be placed on the opposite sides of the product molecule. Conrotatory motion could not place the in-phase lobes together, i.e., it does not lead to bonding interaction and also the process is symmetry forbidden, i.e., the product is *m*-asymmetric. Therefore, ring-closure does not take place by this fashion.



(2*E*, 4*Z*)-2,4-Hexadiene

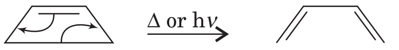
trans-3,4-Dimethylcyclobutene

ψ_3^*
Excited state HOMO
(*m*-symmetry)

(*m*-symmetry)

Thus, stereochemically different products are obtained on thermal and photochemical cyclization of the same substrate.

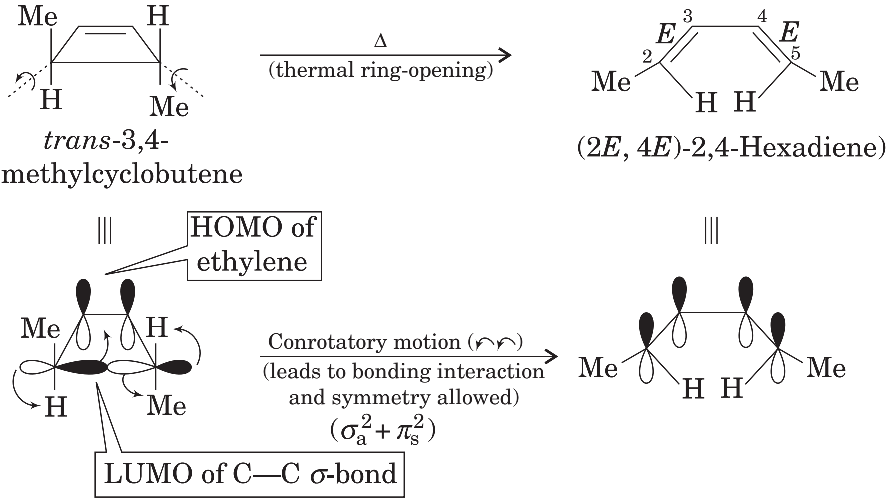
2. Electrocyclic ring-opening reactions given by cyclobutene and its derivatives The opening of cyclobutene ring leading to the formation of 1,3-butadiene may be designated as [$\sigma^2 + \pi^2$] ring opening because two electrons of C—C σ-bond and two electrons of C═C π-bond are involved in this process.



Cyclobutene 1,3-Butadiene

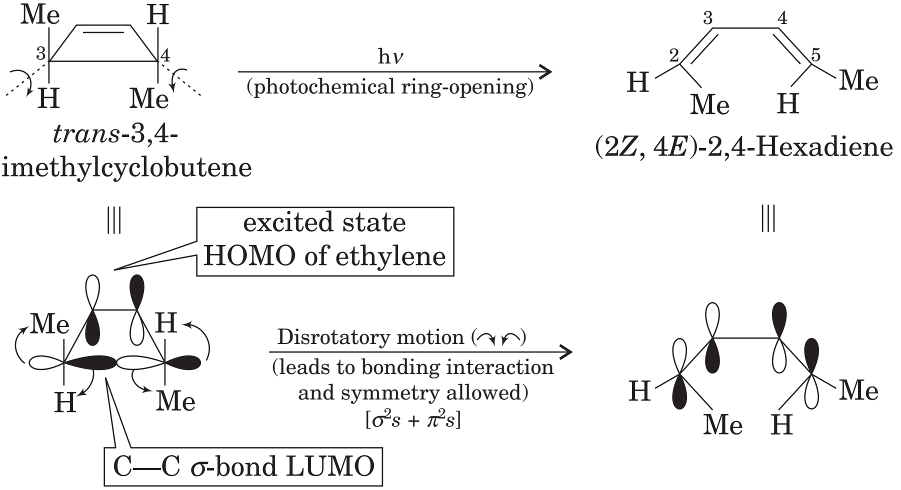
Thermal ring-opening of *trans*-3,4-dimethylcyclobutene During thermal ring opening, the LUMO of the C—C σ-bond interacts with the ground-state HOMO of the C═C bond (π of ethylene) in order to have a bonding interaction (in-phase overlap) with the *p*-orbitals of the alkene part. It requires a conrotatory ring-opening (a disrotatory motion causes out-of-phase overlap). Thus, when *trans*-3,4-dimethylcyclobutene is heated, (2*E*, 4*E*)-2,4-

hexadiene is obtained. It is to be noted that on energy consideration, the σ part of the molecule (i.e., the C—C σ-bond) which is less likely to be excited to its first excited state is used as the LUMO and the higher energy part (π part) which is more likely to be excited to its first excited state is used as the HOMO.



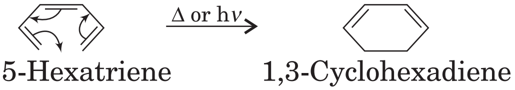
The other mode of conrotatory motion (↷↷) is less preferred because the transition state is destabilized by the steric interaction between the two methyl groups.

Photochemical ring-opening of trans-3,4-dimethylcyclobutene During photochemical ring-opening, the C—C σ-bond LUMO interacts with the excited state HOMO of the alkene part (i.e., π of ethylene system) in order to have in-phase overlap of the p-orbitals. It requires a disrotatory ring-opening (a conrotatory motion causes out-of-phase overlap). Thus, when *trans*-3,4-dimethylcyclobutene is subjected to photo-induced ring opening, (2*Z*, 4*E*)-2,4-hexadiene is obtained.

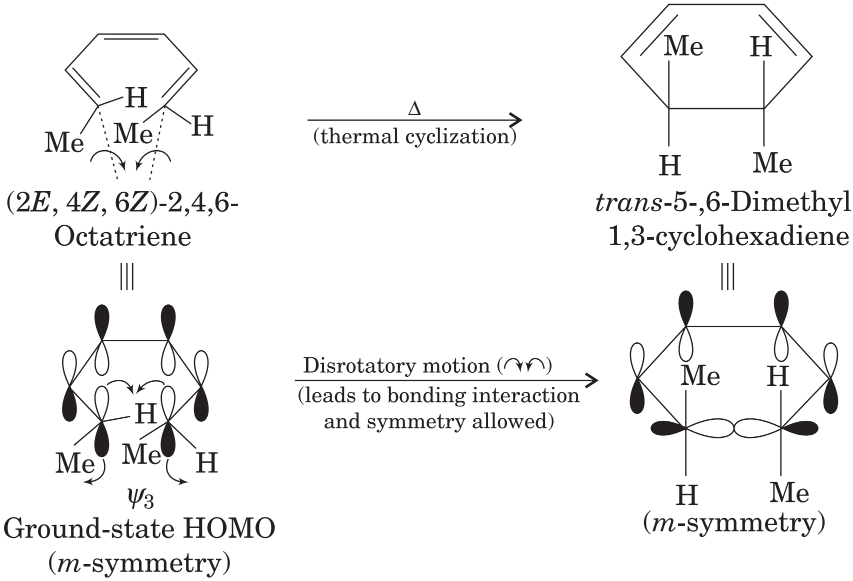


8.2.1.2 *Cyclization of (4n + 2)π Systems*

1. Electrocyclic ring-closure reactions given by 1,3,5-hexatriene and its derivatives 1,3,5-Hexatriene is the most simple example of a polyene having $(4n + 2)\pi$ electrons. As it contains 6π electrons, n is equal to 1. On ring closure, it forms 1,3-cyclohexadiene.

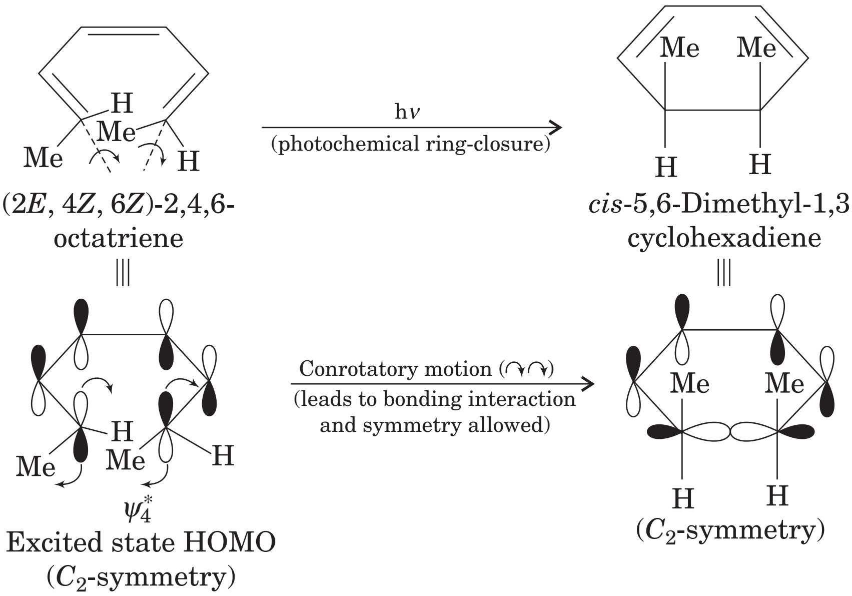


Thermal cyclization of (2*E*, 4*Z*, 6*Z*)-2,4,6-Octatriene For thermal cyclization, the ground state HOMO of the triene, i.e., ψ_3 is to be considered. Since this MO has *m*-symmetry, a disrotatory ring-closure that leads to bonding interaction gives the product. Thus, when (2*E*, 4*Z*, 6*Z*)-2,4,6-octatriene is heated, *trans*-5,6-dimethyl-1,3-cyclohexadiene is obtained and this is because disrotatory motion causes the two methyl groups to be placed on the different sides of the cyclic product molecule. Conrotatory motion could not place the in-phase lobes together, i.e., it does not lead to bonding-interaction and also the process is symmetry forbidden, i.e., the product is *m*-asymmetric. Therefore, ring-closure does not take place by this fashion.

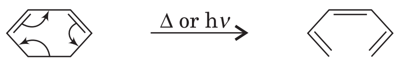

H
Me
Me
H
Δ
(thermal cyclization)
Me
H
H
Me
(2E, 4Z, 6Z)-2,4,6-Octatriene
trans-5-,6-Dimethyl-1,3-cyclohexadiene
|||
|||
H
Me
Me
H
Disrotatory motion
(leads to bonding interaction and symmetry allowed)
Me
H
H
Me
ψ3
Ground-state HOMO
(m-symmetry)
(m-symmetry)

Photochemical cyclization of (2*E*, 4*Z*, 6*Z*)-2,4,6-octatriene In the case of photochemical cyclization, the first excited state ψ_4^* of 1,3,5-hexatriene is to be considered as HOMO because photochemical irradiation causes one electron to be shifted from ψ_3 to ψ_4^*. Since

ψ_4^* has C_2-symmetry, therefore, a conrotatory motion is required for bonding overlap leading to the formation of the σ-bond. Thus, when (2*E*, 4*Z*, 6*Z*)-2,4,6-octatriene is subjected to photochemical cyclization, *cis*-5,6-dimethyl-1,3-cyclohexadiene is obtained and this is because conrotatory motion causes the two methyl groups to be placed on the same side of the cyclic product. The disrotatory motion is symmetry forbidden, and therefore, ring closure does not take place by this fashion.

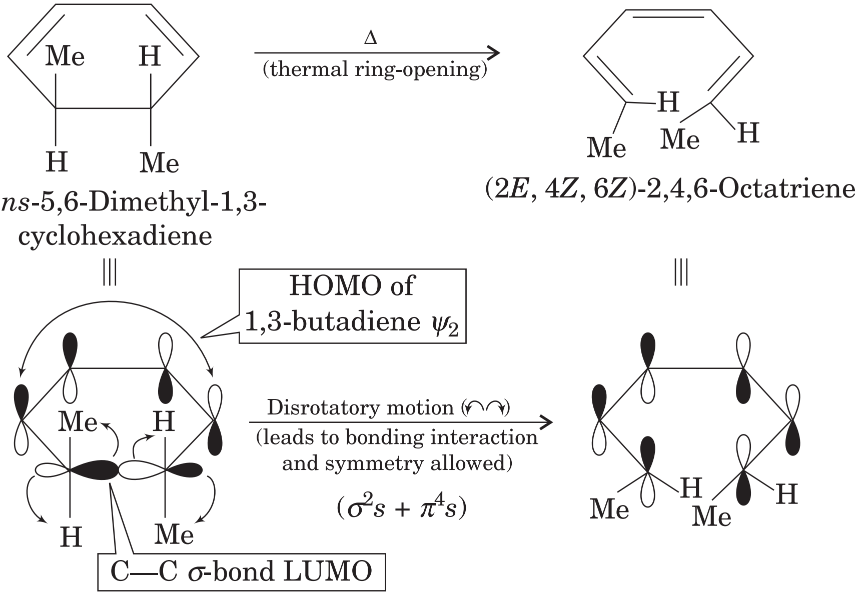

H
Me
Me
H
(2E, 4Z, 6Z)-2,4,6-octatriene
hν
(photochemical ring-closure)
Me Me
H H
cis-5,6-Dimethyl-1,3-cyclohexadiene
|||
|||
H
Me
Me
H
ψ_4^*
Excited state HOMO
(C_2-symmetry)
Conrotatory motion
(leads to bonding interaction and symmetry allowed)
Me Me
H H
(C_2-symmetry)

2. Electrocyclic ring-opening reactions given by 1,3-cyclohexadiene and its derivatives The opening of cyclohexadiene ring leading to the formation of 1,3,5-hexatriene may be designated as [$\sigma^2 + \pi^4$] ring opening because two electrons of the C—C σ-bond and four electrons of two C=C π-bonds are involved in this process.

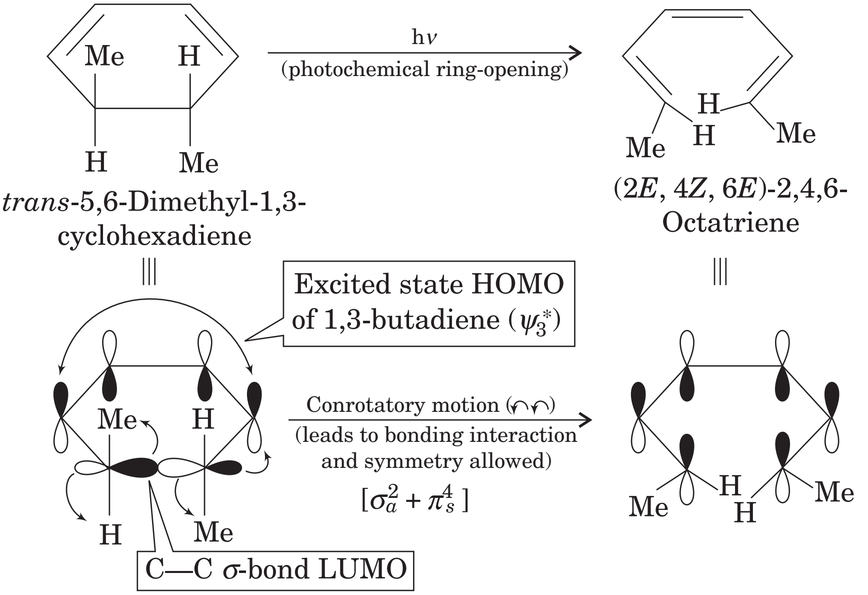


1,3-Cyclohexadiene 1,3,5-Hexatriene

Thermal ring-opening of trans-5,6-dimethyl-1,3-cyclohexadiene During thermal ring opening, the C—C σ-bond LUMO interacts with the HOMO of 1,3-butadiene (ψ_2) in order to have a bonding interaction (in-phase overlap) with the *p*-orbitals of the alkene part in the product triene. It requires a disrotatory ring-opening (a conrotatory motion causes out-of-phase overlap). Thus, when *trans*-5,6-dimethyl-1,3-cyclohexadiene is heated. (2*E*, 4*Z*, 6*Z*)-2,4,6-octatriene is obtained.


Me
H
H
Me
Δ
(thermal ring-opening)
H
Me
Me
H
trans-5,6-Dimethyl-1,3-cyclohexadiene
(2E, 4Z, 6Z)-2,4,6-Octatriene
HOMO of 1,3-butadiene ψ_2
Me
H
H
Me
Disrotatory motion
(leads to bonding interaction and symmetry allowed)
$(\sigma^2 s + \pi^4 s)$
C—C σ-bond LUMO
Me
H
Me
H

Photochemical ring-opening of trans-5,6-dimethyl-1,3-cyclo-hexadiene In photochemical ring-opening, the C—C σ-bond HOMO interacts with excited state HOMO of 1,3-butadiene system in order to have in-phase overlap of *p*-orbitals. It requires a conrotatory ring-opening (a disrotatory motion causes out of phase overlap). Thus, when *trans*-5,6-dimethyl-1,3-cyclohexadiene is subjected to photo-induced ring-opening, (2*E*, 4*Z*, 6*E*)-2,4,6-octatriene is obtained.


Me
H
H
Me
hν
(photochemical ring-opening)
H
H
Me
Me
trans-5,6-Dimethyl-1,3-cyclohexadiene
(2E, 4Z, 6E)-2,4,6-Octatriene
Excited state HOMO of 1,3-butadiene (ψ_3^*)
Me
H
H
Me
Conrotatory motion
(leads to bonding interaction and symmetry allowed)
$[\sigma_a^2 + \pi_s^4]$
C—C σ-bond LUMO
Me
H
H
Me

[The other mode of conrotatory motion (↷↷) is less preferred because the transition state is destabilized by the steric interaction between the two methyl groups.)

8.2.2 Woodward and Hoffmann Selection Rules for Electrocyclic Reactions

The HOMOs of the linear conjugated polyene systems have alternating symmetry properties. On the basis of this, Woodward and Hoffmann were able to propose the selection rules for electrocyclic reactions which may be given as follows:

All conjugated polyenes having 4n or (4n + 2) electrons and with HOMOs having C_2 symmetry will undergo electrocyclic ring-closure or ring-opening reactions by conrotatory motion and with HOMOs having plane of symmetry (m) will undergo electrocyclic ring-closure or ring-opening reactions by disrotatory motion.

Number of electrons involved	Mode of activation	Symmetry of HOMO	Allowed mode of rotation	Stereochemistry of the reactant and product
$4n$ (n = 1, 2, 3 etc.)	Thermal (Δ)	C_2	Conrotatory	E, Z or $Z, E \rightleftarrows$ *cis*
				Z, Z or $E, E \rightleftarrows$ *trans*
	Photochemical (hν)	m	Disrotatory	E, Z or $Z, E \rightleftarrows$ *trans*
				Z, Z or $E, E \rightleftarrows$ *cis*
$4n + 2$ (n = 1, 2, 3, etc.)	Thermal (Δ)	m	Disrotatory	E, Z or $Z, E \rightleftarrows$ *trans*
				Z, Z or $E, E \rightleftarrows$ *cis*
	Photochemical (hν)	C_2	Conrotatory	E, Z or $Z, E \rightleftarrows$ *cis*
				Z, Z or $E, E \rightleftarrows$ *trans*

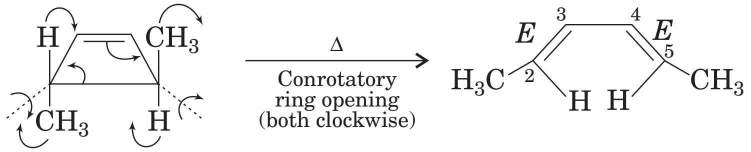
All electrocyclic reactions are, therefore, allowed.

SOLVED PROBLEMS

1. **In thermal ring opening of *trans*-3,4-dimethylcyclobutene, two isomeric products are expected to be formed by the allowed conrotatory mode of rotation. However, only one product is obtained. Explain this observation.**

Solution The two possible conrotatory mode of ring-opening of *trans*-3,4-dimethylcyclobutene leading to the formation of two stereochemically different products are as follows:

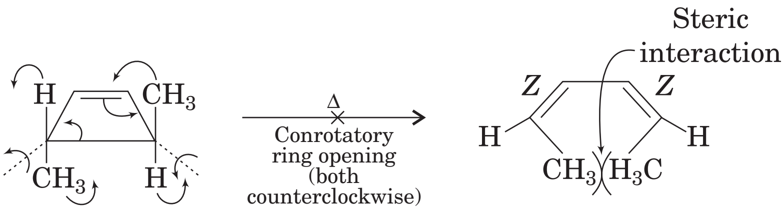
(a)



trans-3,4-Dimethylcyclobutene

(2*E*, 4*E*)-2-4-Hexadiene
(100%)

(b)

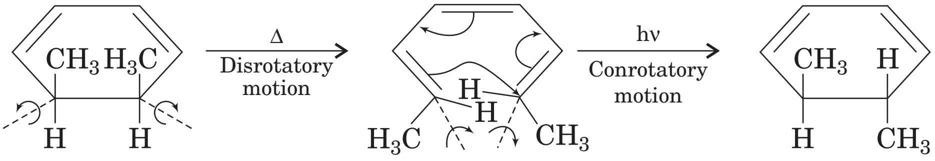


(2*Z*, 4*Z*)-2-4-Hexadiene
(not obtained)

The ring opening mode (a) gives a diene in which the two terminal methyl group are further apart and there is no question of steric interaction between them. So, the transition state leading to (2*E*, 4*E*)-2,4-hexadiene is relatively more stable and the reaction takes place readily to give the product. The ring opening mode (b) is expected to give an isomeric diene in which the two methyl groups are very close and involved in severe steric interaction. So, the transition state leading to (2*Z*, 4*Z*)-2,4-hexadiene is much less stable and for this reason, the reaction does not proceed through this mode of rotation to give this diene. Therefore, (2*E*, 4*E*)-2,4-hexadiene is the only product obtained in this reaction.

2. **Suggest a stereospecific method for converting *cis*-5,6-dimethyl-1,3-cyclohexadiene into its *trans*-isomer.**

Solution When heated, *cis*-5,6-dimethyl-1,3-cyclohexadiene, a 6 electron system [$(4n + 2)\pi$, where $n = 1$], undergoes disrotatory ring opening reaction to give (2*E*, 4*Z*, 6*E*)-2,4,6-octatriene predominantly. This, when irradiated, undergoes conrotatory ring closure to give *trans*-5,6-dimethyl-1,3-cyclohexadiene.



cis-5,6-Dimethyl-1,3-cycohexadiene

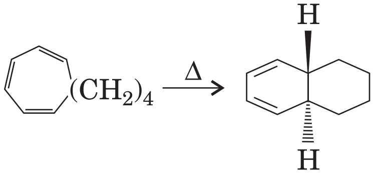
(2*E*, 4*Z*, 6*E*)-2,4, 6-Octatriene

trans-5,6-Dimethyl 1,3-cyclohexadiene

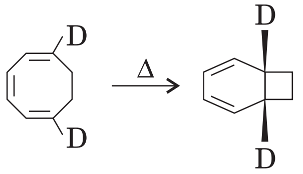
This conversion can also be effected by carrying out photochemical ring-opening followed by thermal ring-closure.

3. **Which of the following electrocyclic reactions in expected to take place readily by a concerted mechanism thermally?**

(a)



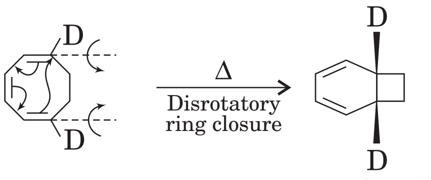
(b)



Solution

(a) Formation of *trans*-product requires conrotatory motion of the terminal *p*-orbitals. Since cyclization by this mode is not thermally allowed for $(4n + 2)\pi$ electron system, the reaction will not take place readily by a concerted mechanism.

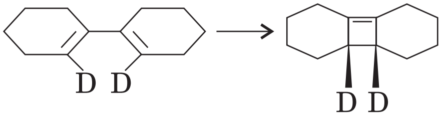
(b) Formation of *cis*-product requires disrotatory motion of the terminal *p*-orbitals. Since disrotation is thermally allowed for $(4\pi + 2)\pi$ electron system, the reaction is expected to take place readily by concerted mechanism.



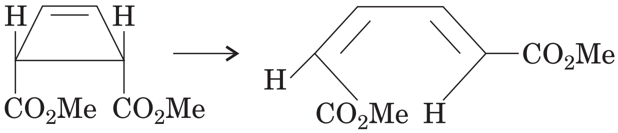
cis-fused

4. Examine the stereochemistry of the product molecule and indicate whether conrotatory or disrotatory ring opening or ring closure has taken place in each of the following reactions. Also, predict the mode of activation (Δ or hν) in each case.

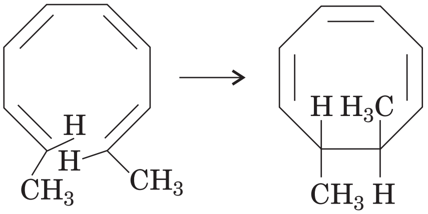
(a)



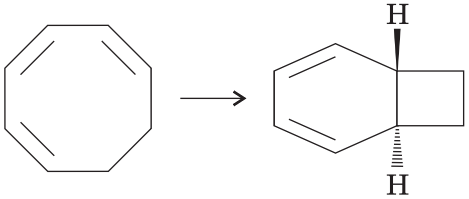
(b)



(c)

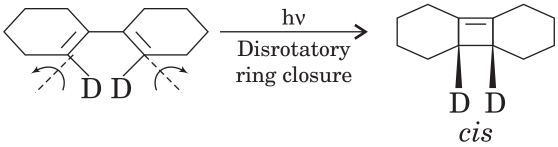


(d)

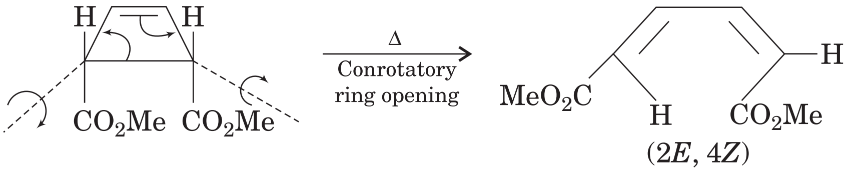


Solution

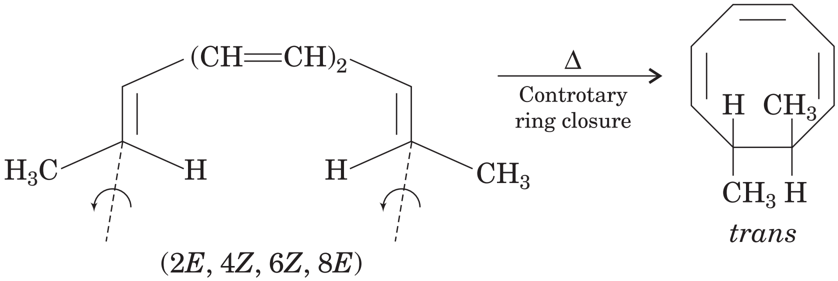
(a) The ring closure has taken place by disrotatory motion because the reaction gives a *cis*-product. Since it is a 4π electron system ($4n\pi$, where $n = 1$), disrotatory mode of ring closure is photochemically allowed.



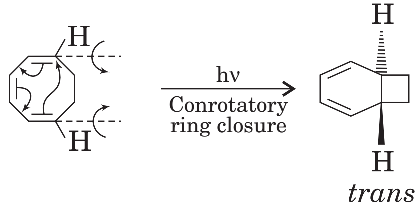
(b) The ring opening has taken place by conrotatory motion because the *cis*-alkene gives (*E*, *Z*)-product. Since it is a $4n$ electron system where $n = 1$, conrotatory ring opening is thermally allowed.



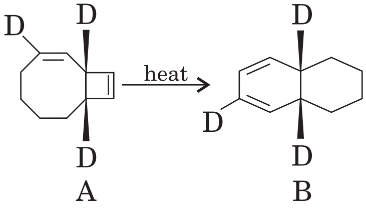
(c) The ring closing has taken place by conrotatory motion because (2*E*, 4*Z*, 6*Z*, 8*E*)-tetraene produces *trans*-product.



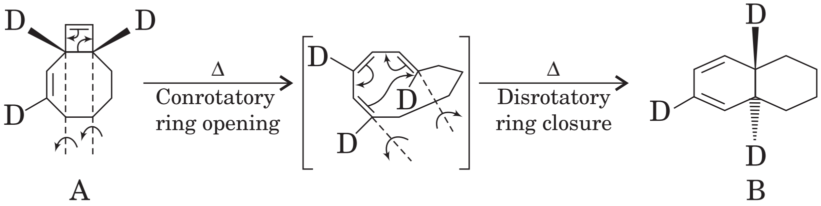
(d) The ring closure has taken place by conrotatory motion because the *trans*-product is obtained from the triene and since it is 6π electron system [$(4n + 2)\pi$, where $n = 1$], conrotatory ring closure is photochemically allowed.



5. Explain the following observation:

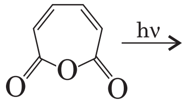


Solution When the compound A (a $4n$ electron system, where $n = 1$) is heated, it undergoes conrotatory ring opening to a cyclodecatriene containing two *cis* and one *trans* double bond. This intermediate triene being a 6π electron system [$(4n + 2)\pi$, where $n = 1$] then undergoes disrotatory ring closure to give the compound B.

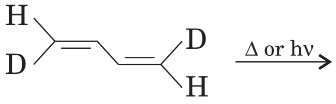


6. Predict the products of the following electrocyclic reactions:

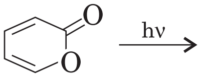
(a)



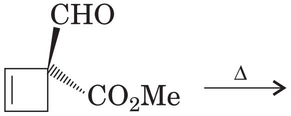
(b)



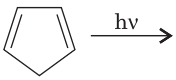
(c)



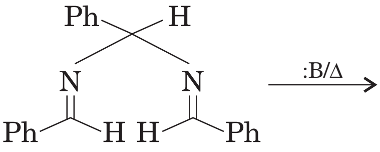
(d)



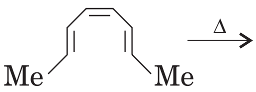
(e)



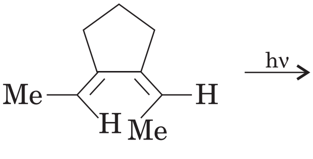
(f)



(g)

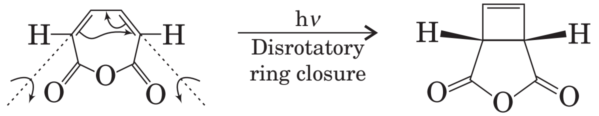


(h)

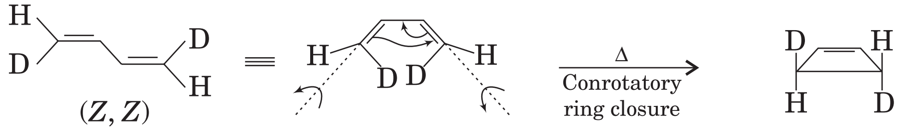


Solution

(a) Since the compound is a $4n\pi$ electron system (where $n = 1$), it undergoes photochemical ring closure by the allowed disrotatory motion to give a *cis*-fused bicyclic compound.

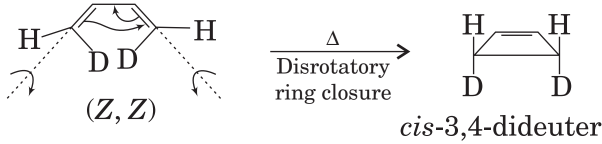


(b) Since the compound is a $4n\pi$ electron system (where $n = 1$), it undergoes thermal ring closure by the allowed conrotatory motion to give *trans*-3,4-dideuteriocyclobutene.



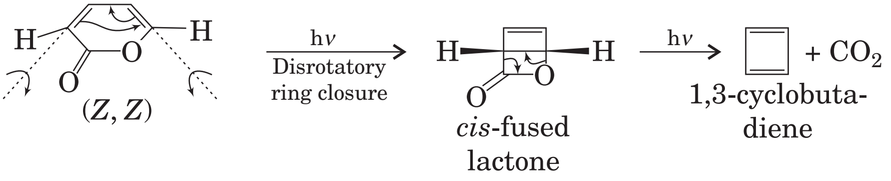
trans-3,4-dideuterio-cyclobutene

However, the compound undergoes photochemical ring closure by the allowed disrotatory motion to give *trans*-3,4-dideuteriocyclobutene.

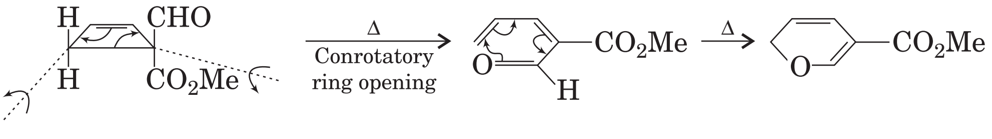


cis-3,4-dideuterio-cyclobutene

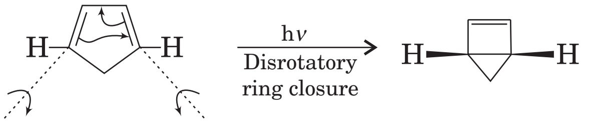
(c) When this $4n\pi$ electron system (where $n = 1$) is irradiated, it undergoes allowed disrotatory ring closure to give a *cis*-fused bicyclic lactone. The lactone undergoes photo-induced decarboxylation by disrotatory ring opening to give 1,3-cyclobutadiene and CO_2.



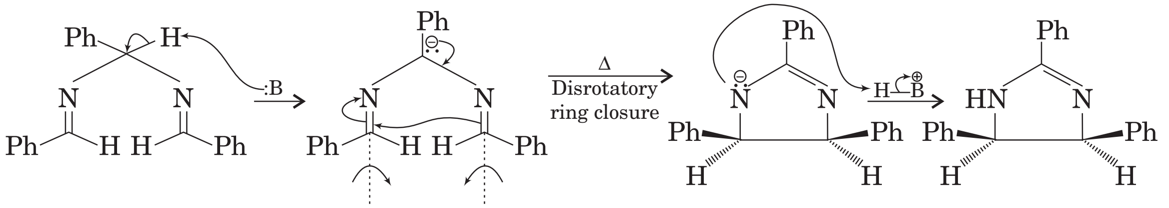
(d) Being a $4n$ electron system (where $n = 1$) this cyclobutene derivative undergoes thermal ring opening by the allowed conrotatory motion to give an α,β-unsaturated carbonyl compound with E stereochemistry of the double bond. The resulting compound [a $(4n + 2)\pi$ electron system, where $n = 1$] undergoes electrocyclic ring closing to give a cyclic ether.



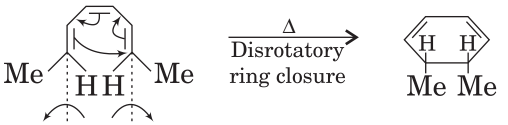
(e) Since the compound is $4n\pi$ electron system (where $n = 1$), it undergoes photochemical ring closure by the allowed disrotatory motion to give a *cis*-fused bicyclic compound.



(f) The base (:B) abstracts a proton from this compound to give its conjugate base which is a 6π electron system [a $(4n + \pi)$ electron system, where $n = 1$]. This undergoes thermally allowed disrotatory ring closure followed by proton take up to give the product.



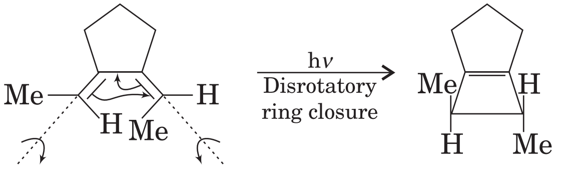
(g) Since the compound is a 6π electron system [*a* $(4n + 2)\pi$ electron system, where $n = 1$], it undergoes thermal ring closure by the allowed disrotatory motion to give *cis*-5,6-dimethyl-1,3-cyclohexadiene.



(2*E*, 4*Z*, 6*E*)-2,4,6-Octatriene

cis-5,6-Dimethyl-1,3-cyclohexadiene

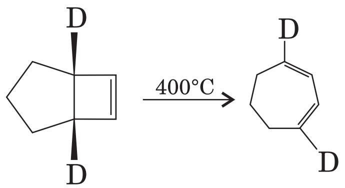
(h) When this $4n\pi$ electron system (where $n = 1$) is irradiated, it undergoes allowed disrotatory ring closure to give a bicyclic compound in which the two methyl groups are oriented *trans* to each other.



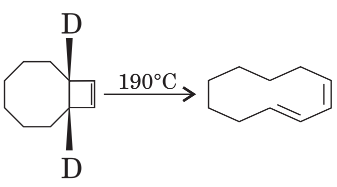
(*E*, *E*) *trans*

7. Explain why the first reaction requires a much higher temperature compared to the second reaction:

(a)

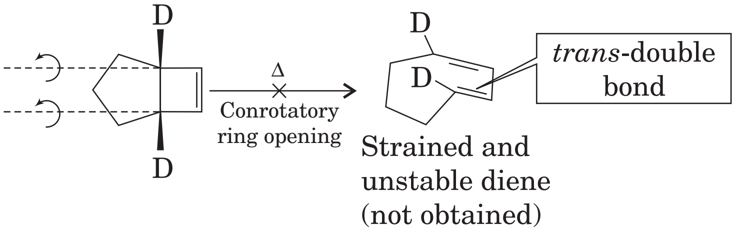


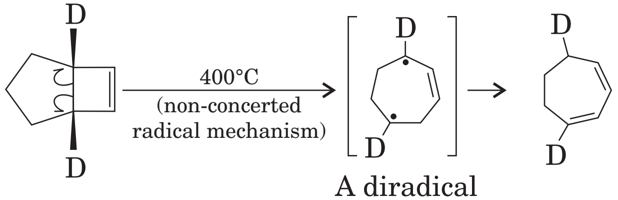
(b)



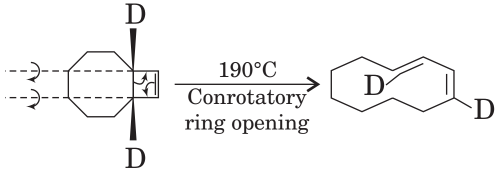
Solution

(a) This bicyclic compound does not undergo thermal ring opening reaction through the symmetry-allowed conrotatory pathway because this would give a highly strained (*E*, *Z*)-diene which, due to presence of a *trans*-double bond in a small ring, is thermodynamically much less stable. However, the thermal ring opening takes place at a higher temperature by a symmetry forbidden disrotatory pathway involving a non-concerted biradical mechanism.



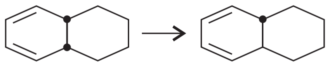


(b) This bicyclic compound undergoes thermal ring opening by the symmetry-allowed conrotatory path relatively smoothly because the resulting 10-membered ring can easily accommodate a *trans*-double bond. This concerted symmetry-allowed reaction, therefore, requires a low temperature.

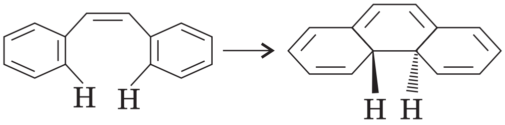


8. How would you carry out the following transformation?

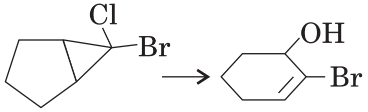
(a)



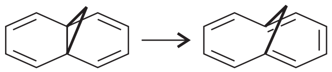
(b)



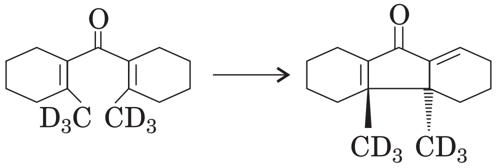
(c)



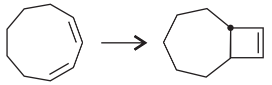
(d)



(e)

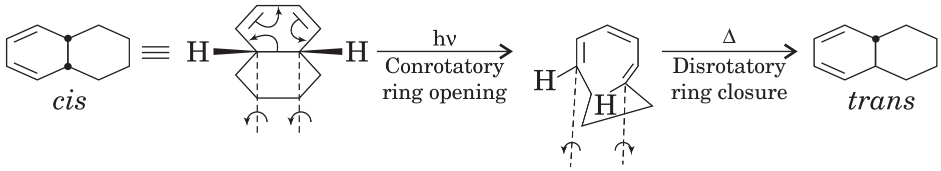


(f)

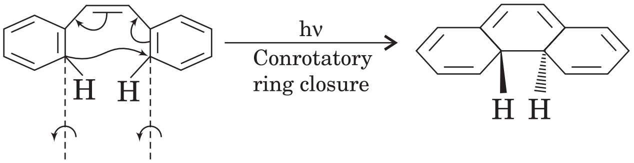


Solution

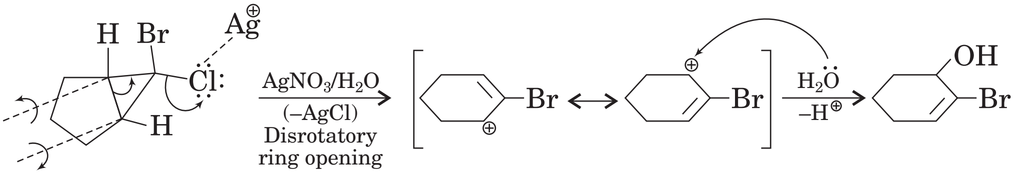
(a) Photochemical ring opening of the *cis*-fused bicyclic compound [*a* (4*n* + 2) electron system, where *n* = 1] by conrotatory mode followed by thermal ring closure of the intermediate by disrotatory mode leads to the formation of isomeric *trans*-fused compound.



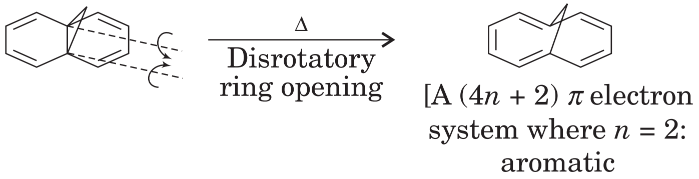
(b) Since the product has hydrogens *trans*- to each other the rotation must have taken place by the conrotatory fashion. Therefore, this ring closing reaction involving 6π electrons [*a* (4*n* + 2)π electron, where *n* = 1] can be carried out by photochemical activation (h*ν*).



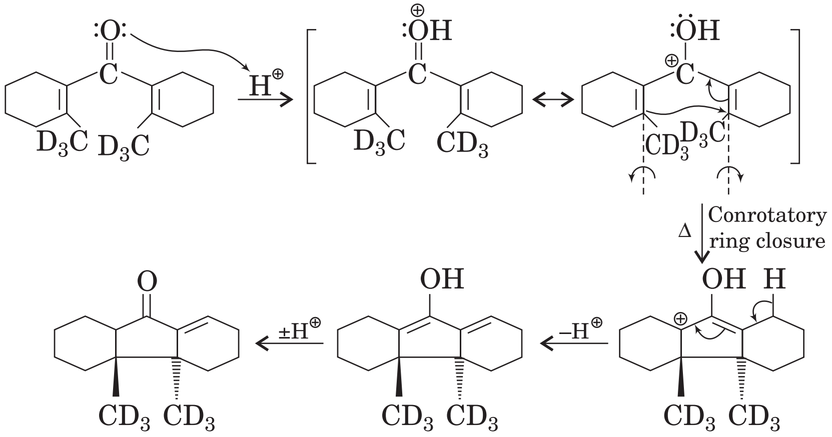
(c) This transformation may be carried out by treating the dihalide with $AgNO_3$ solution. $Ag^{\oplus}$ ion assisted expulsion of chloride and disrotatory ring opening (thermally allowed process because it is a two-electron system) takes place simultaneously. The allyl cation then undergoes nucleophilic attack by water to give, after proton loss, an alcohol.



(d) This transformation can be carried out by heating the starting compound. A disrotatory ring opening reaction takes place. The reaction is very much favourable because on ring opening the strain in cyclopropane ring is released and at the same time a stable aromatic system is formed. It is to be noted that the rotation will move the C—C bond of the other six-membered ring outward (i.e., the C—C bond of the cyclopropane ring inward) is geometrically feasible.

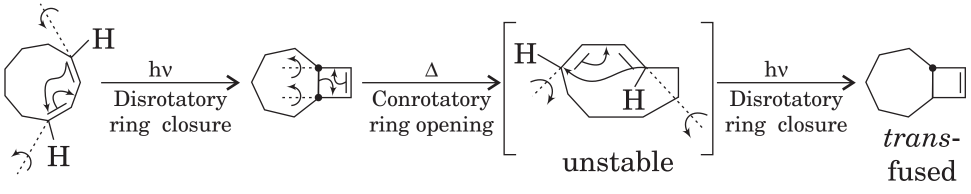


(e) This cyclization reaction takes place when this ketone is heated in the presence of H_3PO_4. The protonated ketone (*a* $4n\pi$ electron system, where n = 1) which is equivalent to a pentadienyl cation, undergoes thermal ring closure by an allowed conrotatory fashion to give a resonance-stabilized carbocation. This on proton loss followed by tautomerization gives a cyclic ketone in which the two $–CD_3$ groups are *trans* to each other.



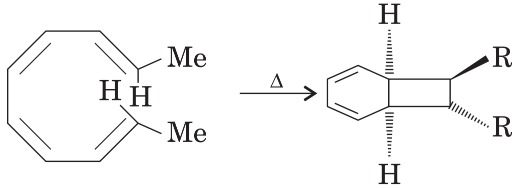
[This ring closure reaction of doubly α,β-unsaturated ketone to give a cyclopentanone system is known as the *Nazarov cyclization*.

(f) When this diene (*a* $4n\pi$ electron system, where n = 1) is irradiated, it undergoes allowed disrotatory ring closure to give a bicyclic compound in which the rings are *cis*-fused. This compound, when heated, undergoes conrotatory ring opening to give an unstable diene having a *trans* double bond. When this diene is irradiated, a disrotatory ring closure takes place to give again a bicyclic compound in which the two rings are *trans*-fused.

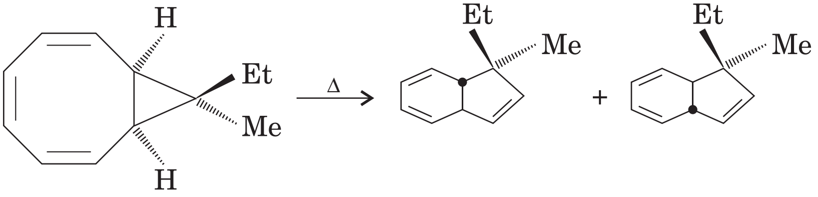


9. Explain the following observations:

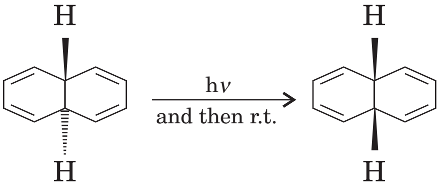
(a)



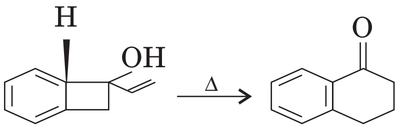
(b)



(c)

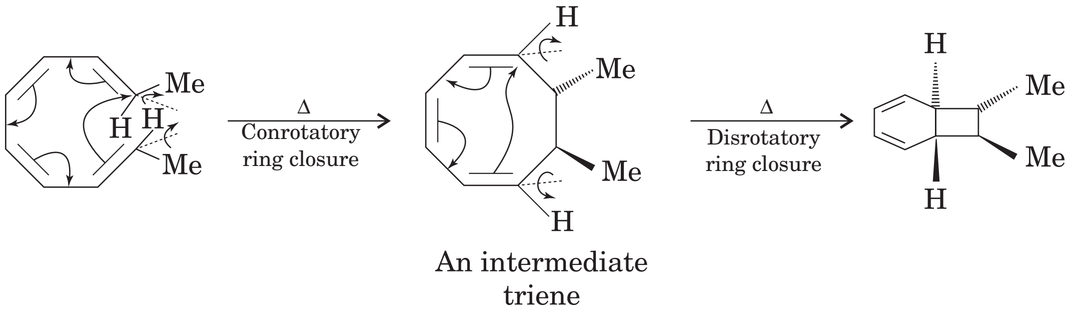


(d)

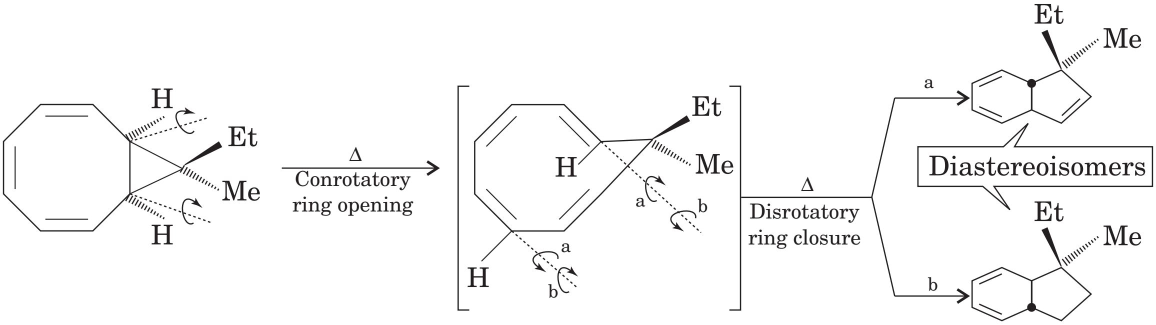


Solution

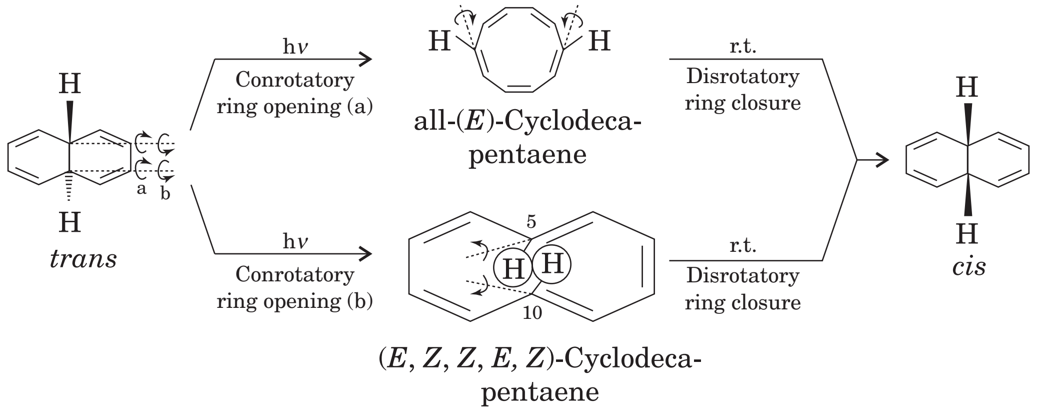
(a) Since this molecule is a tetraene (a $4n\pi$ electron system, where $n = 2$), it undergoes thermal ring closure by conrotatory motion to an intermediate triene in which the two methyl groups are *trans* oriented. This triene [a $(4n + 2)\pi$ electron system, where $n = 1$] undergoes thermal ring closure by disrotatory mode to produce a bicyclic compound in which the two rings are *cis*-fused.



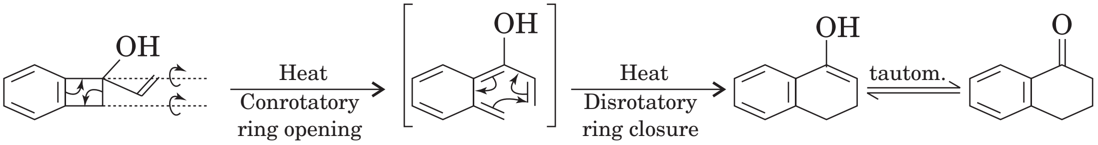
(b) This bicyclic triene (a $4n$ electron system, where $n = 2$) undergoes thermal conrotatory ring opening to give an unstable tetraene with a *trans* double bond. This tetraene then undergoes thermal ring closure by the two disrotatory mode (a and b) to give two diastereomeric products as only 6π electrons are involved.



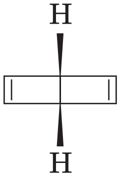
(c) This *trans*-fused bicyclic compound (a 6 electron system) on irradiation undergoes conrotatory ring opening to give all-(E) and (E, Z, Z, E, Z)-isomers of cyclodecapentaene. The first isomer is unstable due to angle strain and the second isomer is unstable due to *trans*-annular interaction (the hydrogens in 5 and 10 positions interfere sterically with each other to make it non-planar and non-aromatic). Both the isomers then undergo disrotatory ring closure at room temperature to give the *cis*-isomer of the starting compound.



(d) The compound (a four-electron system) undergoes thermal conrotatory ring opening to give an enol. This unstable enol (a 6π electron system) undergoes ready disrotatory ring closing to give another enol which tautomerizes to give the corresponding ketone (α-tetralone). Gain of aromaticity is the driving force of the second step reaction.

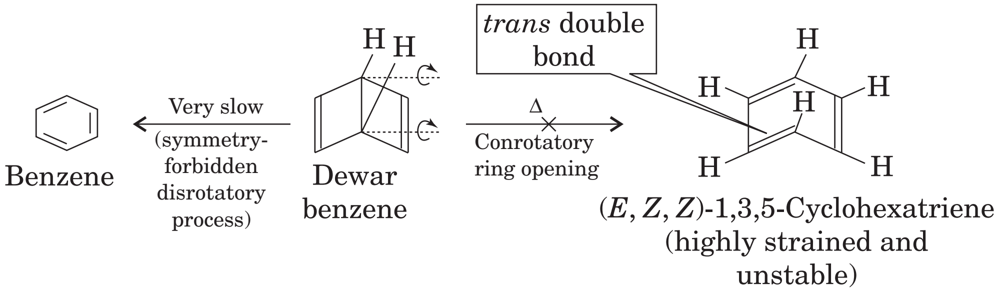


10. Dewar benzene is less stable than its isomer benzene by 60 kcal/mol. Nevertheless, its conversion into benzene is extremely slow with an activation energy of about 37 kcal/mol. Explain this observation.



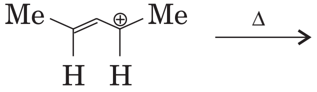
Dewar benzene

Solution The conversion of Dewar benzene into benzene requires opening of a cyclobutene ring (a $4n$ electron system, where $n = 1$). Now, ring opening by the conrotatory mode is symmetry allowed. However, this would result in formation of a 1,3,5-cyclohexatriene containing a *trans* double bond. A six-membered ring cannot accommodate a *trans* double bond due to severe ring strain. Hence, the ring opening of Dewar benzene is a geometrically unfavourable process. The disrotatory ring opening process that would lead directly to benzene, is a thermally forbidden process according to the selection rules. The conversion may take place by non-concerted pathway which is actually very slow. This explains why conversion of Dewar benzene into benzene is extremely slow with activation energy of about 37 kcal/mol.

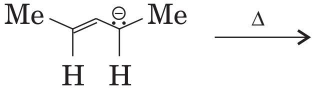

Benzene
Very slow
(symmetry-forbidden disrotatory process)
H H
Dewar benzene
Δ
Conrotatory ring opening
trans double bond
H
H
H
H
H
H
(E, Z, Z)-1,3,5-Cyclohexatriene
(highly strained and unstable)

11. Predict the product in each of the following reactions and explain these by orbital symmetry analysis:

(a)

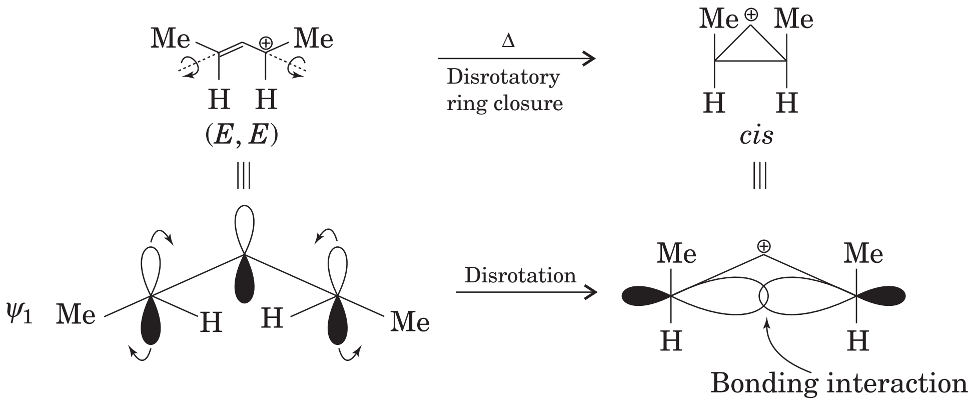


(b)

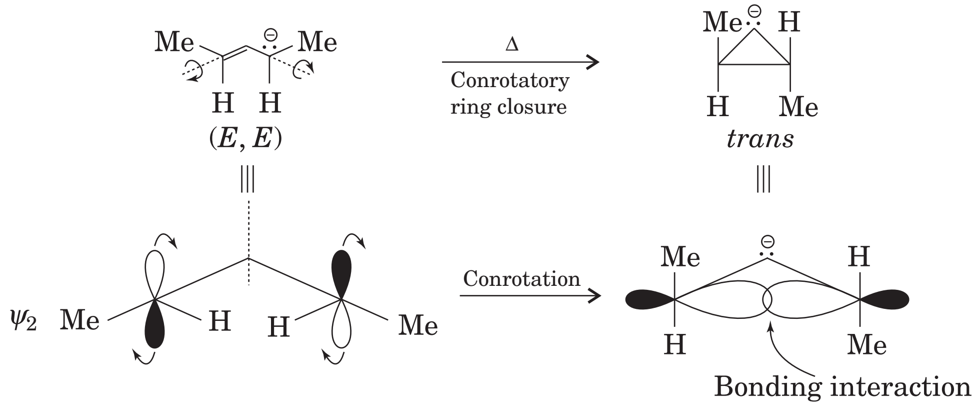


Solution

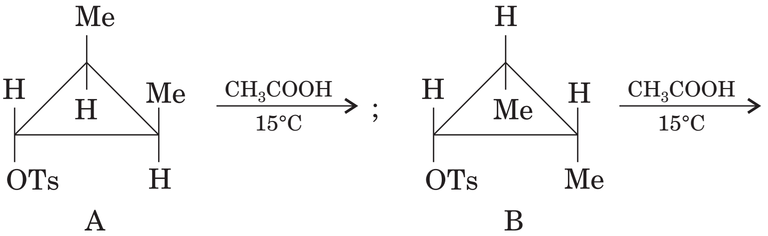
(a) When this allyl cation [a 2π electron system, i.e., a $(4n + 2)\pi$ electron system, where $n = 0$] is heated, it undergoes symmetry-allowed disrotatory ring closure reaction to give a cyclopropyl cation having *cis*-configuration. The HOMO of allyl cation is ψ_1 and therefore, disrotatory motion of the terminal orbitals leads to a bonding interaction.



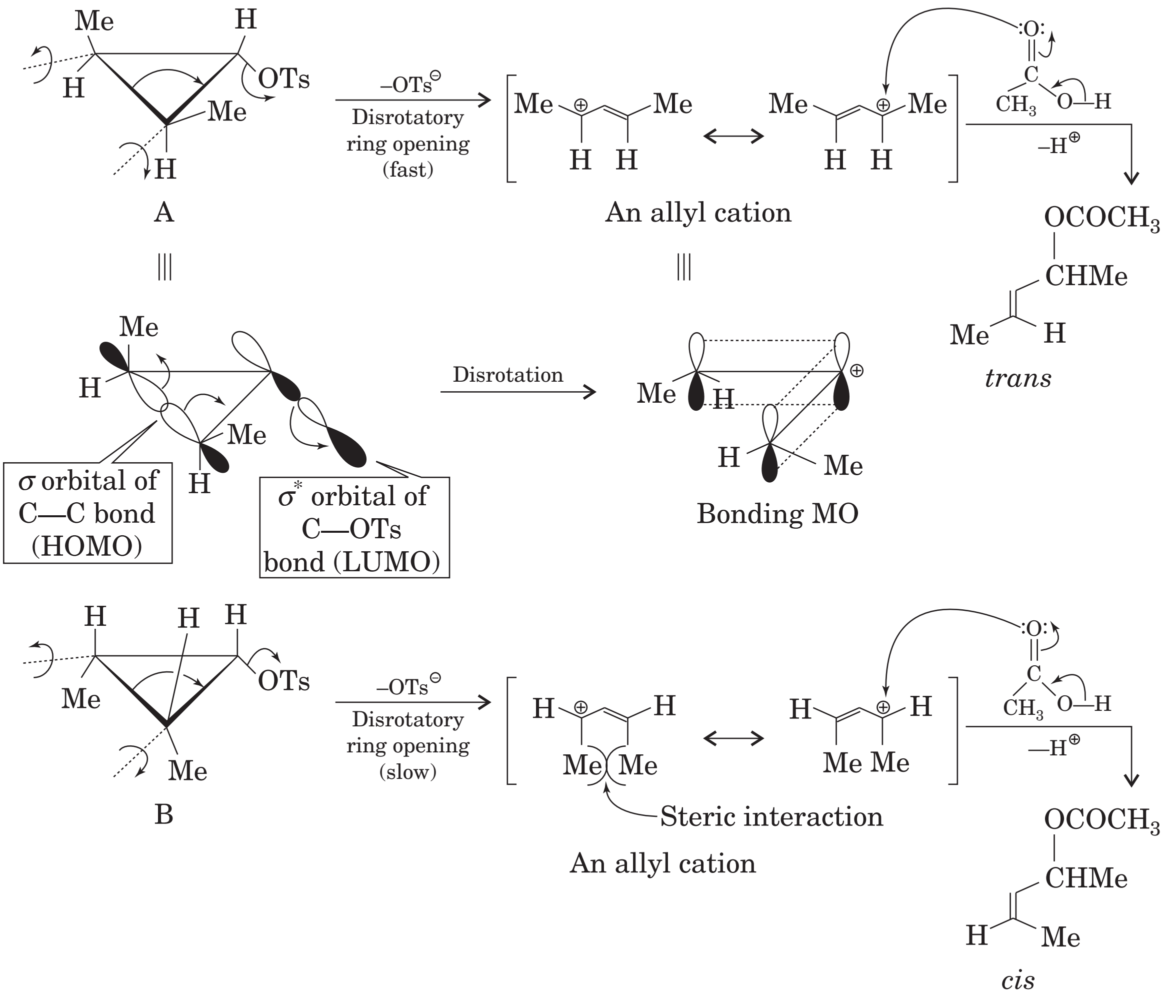
(b) When this allyl anion (a 4π electron system, i.e., a $4n\pi$ electron system, where $n = 1$) is subjected to thermal cyclization, it undergoes symmetry-allowed conrotatory ring closure to give a cyclopropyl anion having *trans*-configuration. The HOMO of the allyl anion is ψ_2, and therefore, conrotatory motion of the terminal orbitals leads to a bonding interaction.



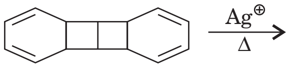
12. Which of the following two reactions (acetolysis) takes place at a faster rate and why?



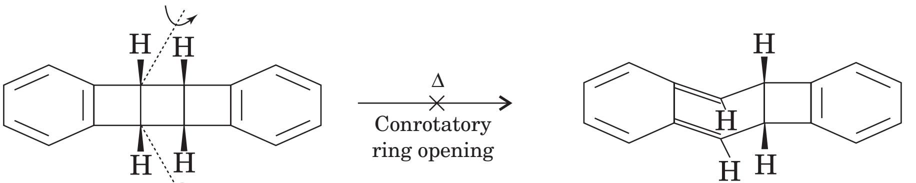
Solution In this solvolysis reaction (S_N1), the loss of $OTs^\ominus$ and ring opening takes place simultaneously to form an allyl cation. Since actually it is an opening of a cyclopropyl cation, it is to be treated as a two-electron system and for this, disrotatory mode of ring opening is thermally allowed. Now, the disrotatory cleavage of the σ-bond must take place in such a fashion that would give an anchimeric assistance to the C—OTs bond cleavage by backside attack. This requires an outward rotation of the two methyl groups in tosylate A and an inward rotation of the two methyl groups in tosylate B. But, because of steric reason (steric interaction between the two methyl groups in the transition state), the tosylate B undergoes ring opening at a much slower rate than the tosylate A. Therefore, acetolysis of the tosylate A takes place at a faster rate than the tosylate B.


A
–OTs⊖
Disrotatory ring opening (fast)
An allyl cation
–H⊕
trans
σ orbital of C—C bond (HOMO)
σ* orbital of C—OTs bond (LUMO)
Disrotation
Bonding MO
B
Disrotatory ring opening (slow)
Steric interaction
An allyl cation
cis

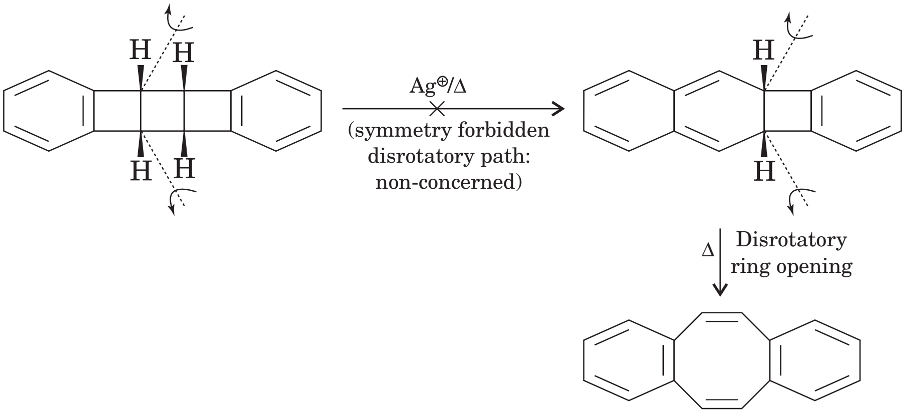
13. Predict the product of the following reaction and explain its formation:



Solution Two consecutive electrocyclic reactions are involved to give the final product. The ring opening of this six-electron system does not take place through the symmetry, allowed conrotatory path because it leads to the formation of highly strained cyclo-hexadiene system with a *trans* double bond (much higher T.S. energy). A thermally forbidden disrotatory ring opening occurs first in the presence of the metal ion which lowers the activation energy for this path. The non-aromatic unstable intermediate (a six-electron system) then undergoes a second ring opening by an allowed disrotatory motion to give the stable aromatic product.

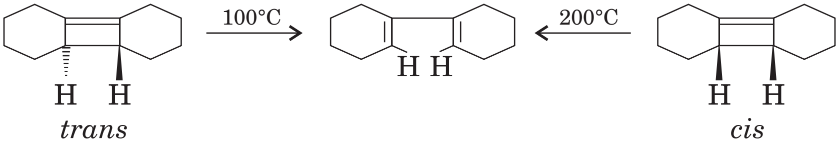


(Unstable and not formed)

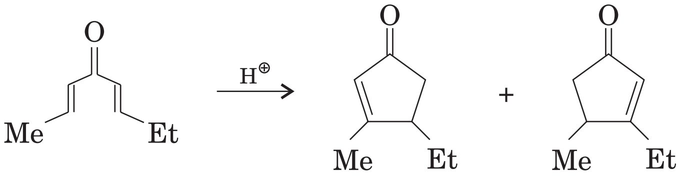


STUDY PROBLEMS

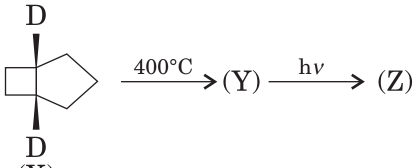
1. Predict the configuration of the product obtained in each of the following electrocyclic reactions:
   (a) (2*E*, 4*E*)-2,4-Hexadiene $\xrightarrow{\Delta}$
   (b) (2*E*, 4*Z*, 6*Z*, 8*E*)-2,4,6,8-Decatetraene $\xrightarrow{\Delta}$
   (c) (2*E*, 4*Z*, 6*E*)-2,4,6-Octatriene $\xrightarrow{h\nu}$
   (d) *cis*-3,4-Dimethylcyclobutene $\xrightarrow{\Delta}$
   (e) *trans*-3,4-Dimethylcyclobutene $\xrightarrow{h\nu}$
2. Explain why the *cis*-isomer requires a much higher temperature compared to the *trans*-isomer for ring opening.



3. Predict the product of the following Nazarov cyclization from FMO considerations:

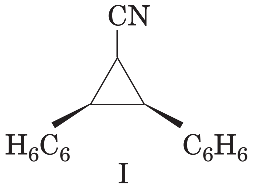


4. The bicyclic compound (X) on thermal ring opening yields (Y) which is contrary to the Woodward–Hoffmann selection rules. The compound (Y) on photochemical ring closing gives the compound (Z). However, (Z) cannot produce (Y) by reversible reaction. Identify.

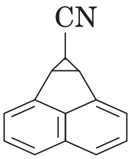


(X)

5. When treated with strong base, the compound I readily undergoes electrocyclic ring opening to the corresponding allyl anion, but the compound II does not. Identify this observation.

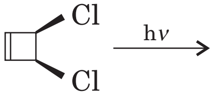


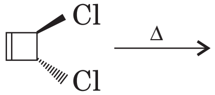
I

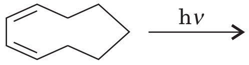


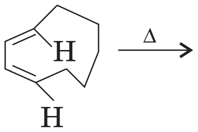
II

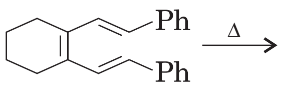
6. Predict the product expected to be formed from each of the following reactions:

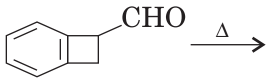
(a) 

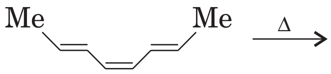
(b) 

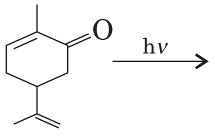
(c) 

(d) 

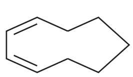
(e) 

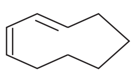
(f) 

(g) 

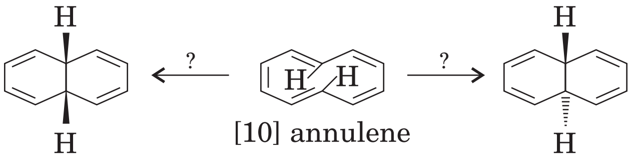
(h) 

7. Both of the following compounds undergo photochemical ring closure reactions. Predict the structure and stereochemistry of the products and explain.


I
(*Z*, *Z*)

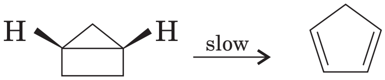

II
(*Z*, *E*)

8. How can you get the two diastereoisomeric bicyclic compounds from the starting [10] annulene?



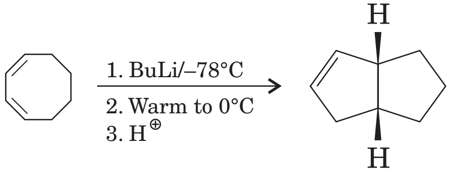
cis [10] annulene *trans*

9. The following bicyclic compound is expected to undergo ready rearrangement to give 1,3-cyclopentadiene. However, this rearrangement is not so fast as to preclude isolation of the compound. Explain this observation.

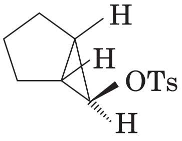


[**Hint:** Conrotatory ring opening leads to the formation of an impossibly strained ring.]

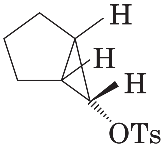
10. Explain the following observation:



11. The compound I undergoes acetolysis at a rate 2×10^6 times faster than the isomeric compound II. Explain.

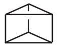


I



II

12. Prismane suffers from tremendous amount of strain. Nevertheless, its transformation to benzene (a stable aromatic system) is not spontaneous. Explain on the basis of FMO theory.

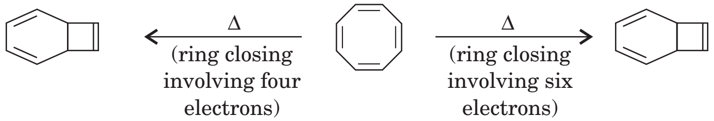


Prismane

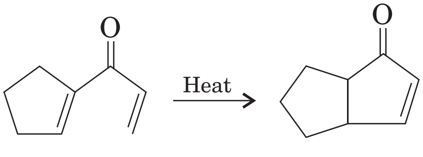
13. Sketch the following π-MOs showing modes: (i) HOMO for 1,3,5-hexatriene and (ii) LUMO for allyl anion.

14. Draw the π-molecular orbitals of penta-2,4-dienyl system (cation, radical and anion). Label the non-bonding MO and indicate the nodes in each MO. Classify each MO as symmetric (S) or antisymmetric (A) with respect to *m* (mirror plane of symmetry).

15. Which of the following reactions is more likely to take place? Give your reasoning.

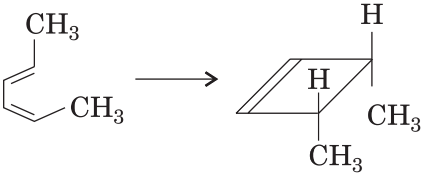


16. Explain the mechanism of the following reaction:

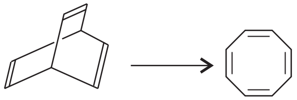


17. How would you carry out the following transformation?

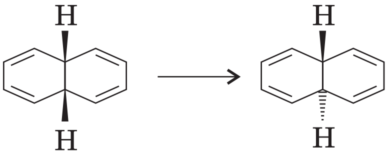
(a)



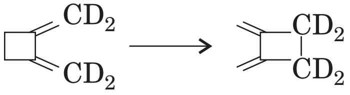
(b)



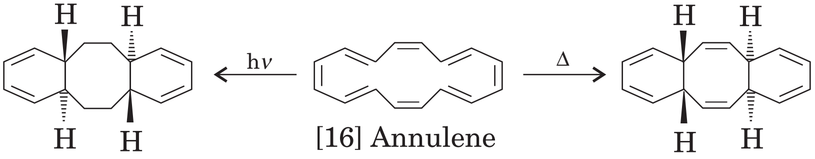
(c)



(d)



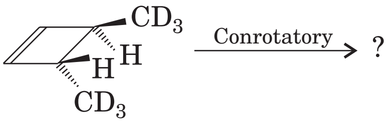
18. Explain the following isomerisations of [16] annulene:



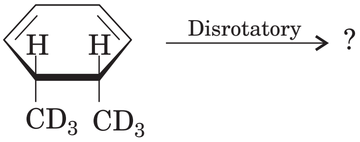
[16] Annulene

19. There are two ways of each of the stereochemical modes in the following electrocyclic transformations. Predict the structure of the preferred product and give your reasoning.

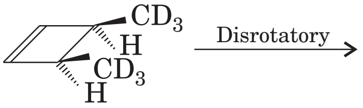
(a)



(b)

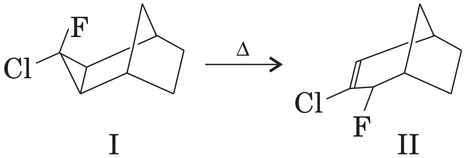


(c)



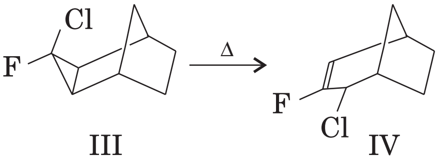
20. Suggest mechanism for the result of pyrolysis of the two isomers (I) and (II) to give (III) and (IV), respectively.

(a)



I II

(b)



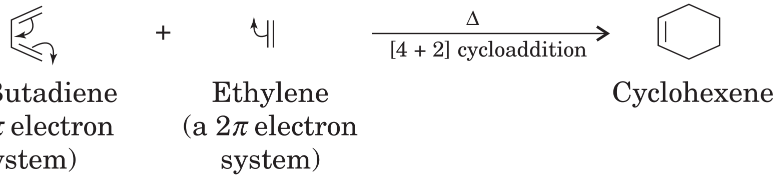
III IV

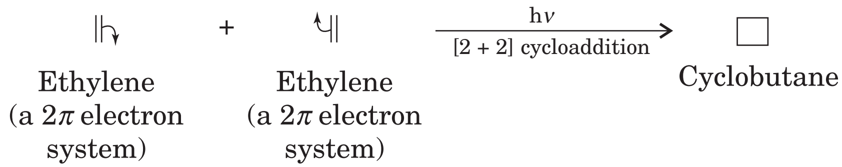
[**Hint:** See the answer to the Solved Problem 12.]

8.3 CYCLOADDITION REACTIONS

Introduction

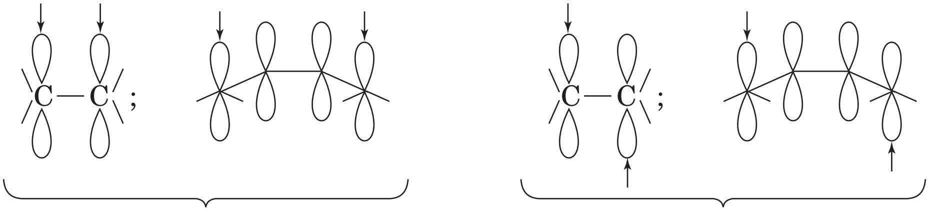
A cycloaddition reaction is one in which two unsaturated molecule or two unsaturated part of a single molecule undergo addition reaction to yield a cyclic product. If the number of π-electrons in the reacting components are 'x' and 'y', respectively, the cycloaddition reaction is called a $[x + y]$ cycloaddition. Therefore, the well-known Diels–Alder reaction in which a diene (a 4π electron system) combines with a dienophile (a 2π electron system) in a [4 + 2] cycloaddition. The dimerizaton of ethylene (a 2π electron system), on the other hand, is a [2 + 2] cycloaddition.





Formation of a cyclic product takes place at the expense of two π bonds (one each of the reacting partners) and gain of two σ bonds at the end of both the components. Thus, in this reaction, there is a loss of two π bonds and gain of two σ bonds. Since σ bonds are stronger than π bonds, the formation of the product is usually favoured energetically.

The stereochemical mode of cyclization Cycloaddition reactions can be classified by it stereo chemistry with respect to the plane of each reacting molecule. A cycloaddition reaction may take place either across the same face or across the opposite faces of the planes in each reacting component. If the reaction takes place across the same face of a π system, the reaction is said to be *suprafacial* with respect to the π system and the reaction is said to be *antarafacial* if the reaction occurs at opposite faces with respect to the π system.

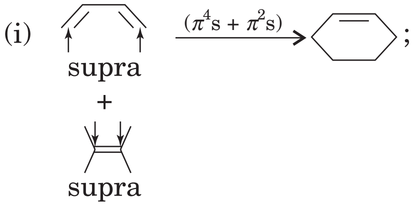


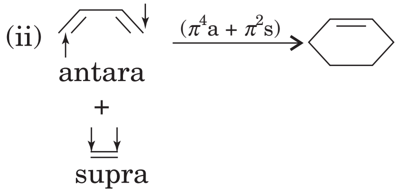
Suprafacial
(just like a *syn*-addition)

Antarafacial
(just like an *anti*-addition)

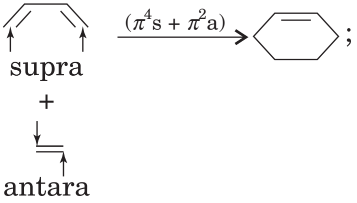
The stereochemical mode is given by a subscript s or a which indicates whether the addition occurs in a suprafacial mode or antarafacial mode on each unit.

The four possible modes of [4 + 2] cycloaddition reaction, for example, are as follows:

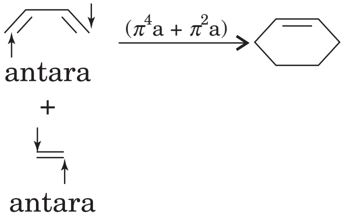




(iii)



(iv)



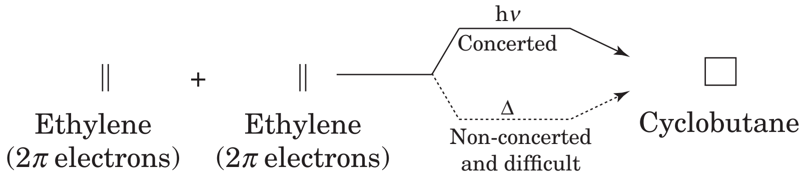
Because of steric reason, *almost all cycloaddition reactions are suprafacial on both the components*.

Symmetry allowed and symmetry forbidden cycloaddition reactions According to the FMO theory, a symmetry-allowed cycloaddition reaction is one in which the HOMO of one component and the LUMO of the other component overlap in the same phase leading to bonding interactions. On the other hand, a symmetry forbidden cycloaddition reaction is one in which HOMO and LUMO overlap in different phases leading to antibonding interaction.

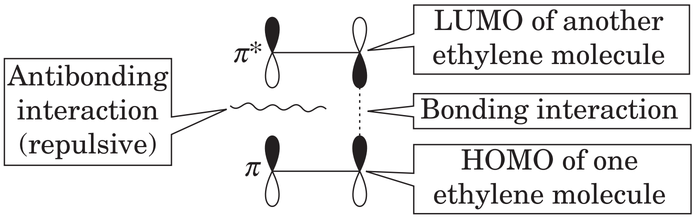
8.3.1 FMO Theory of Cycloaddition Reactions

8.3.1.1 [π^2 + π^2] Cycloaddition Reactions

The [2 + 2] cycloaddition of two ethylene molecules to form a cyclobutane molecule is photochemically allowed but thermally forbidden (i.e., unlikely to take place concertedly).



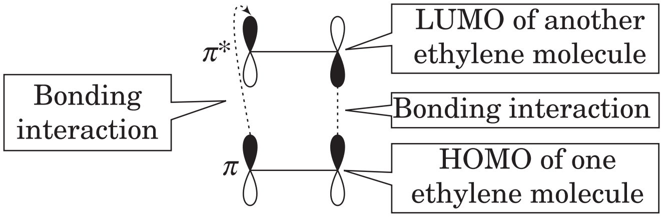
(a) Thermal reaction Thermal reactions involve molecules reacting in the ground state. In [2 + 2] cycloaddition of ethylene, the lobes of HOMO (π MO) in one molecule and that of LUMO (π* MO) of the other does not overlap in a fashion leading to bonding interaction between both sets of carbon atoms. Therefore, the reaction in which both the components react in a suprafacial manner, i.e., a [π^2s + π^2s] addition is thermally forbidden. It means that a thermal cycloaddition between two ethylene molecules is unlikely to take place concertedly. In fact, the reaction actually takes place through a non-concerted free radical mechanism (catalyzed by transition metal complex).



π*
LUMO of another ethylene molecule
Antibonding interaction (repulsive)
Bonding interaction
π
HOMO of one ethylene molecule

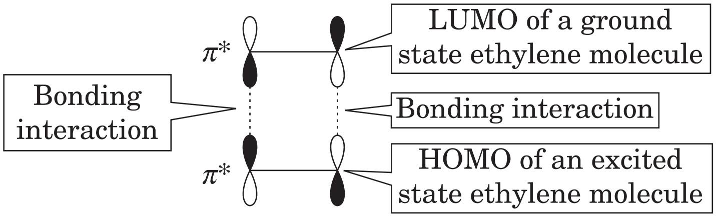
(Thermally forbidden *supra-supra* interaction)

However, a thermal [2 + 2] cycloaddition reaction is expected to take place if it is suprafacial with respect to one component and antarafacial with respect to the other, i.e., if it is a [π^2s + π^2a] process, that leads to bonding interaction. This symmetry-allowed process is, in fact, geometrically very difficult (the energy of the transition state is very high) and so, it does not take place.


π^*
LUMO of another ethylene molecule
Bonding interaction
Bonding interaction
π
HOMO of one ethylene molecule

(Symmetry allowed but geometrically difficult *supra–antara* interaction)

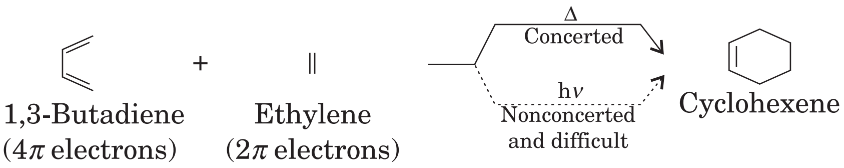
(b) Photochemical reaction When ethylene is irradiated, one of its π electrons is promoted from bonding MO(π) to antibonding MO(π^*). Therefore, the excited state HOMO of ethylene is π^*. In this case, a bonding interaction occurs between the HOMO of an excited state ethylene molecule and the LUMO of a ground state ethylene molecule when the reaction is suprafacial with respect to both the components. Therefore, a [π^2s + π^2s] process is photochemically allowed and occurs readily through a concerted pathway.


π^*
LUMO of a ground state ethylene molecule
Bonding interaction
Bonding interaction
π^*
HOMO of an excited state ethylene molecule

(Photochemically allowed *supra–supra* interaction)

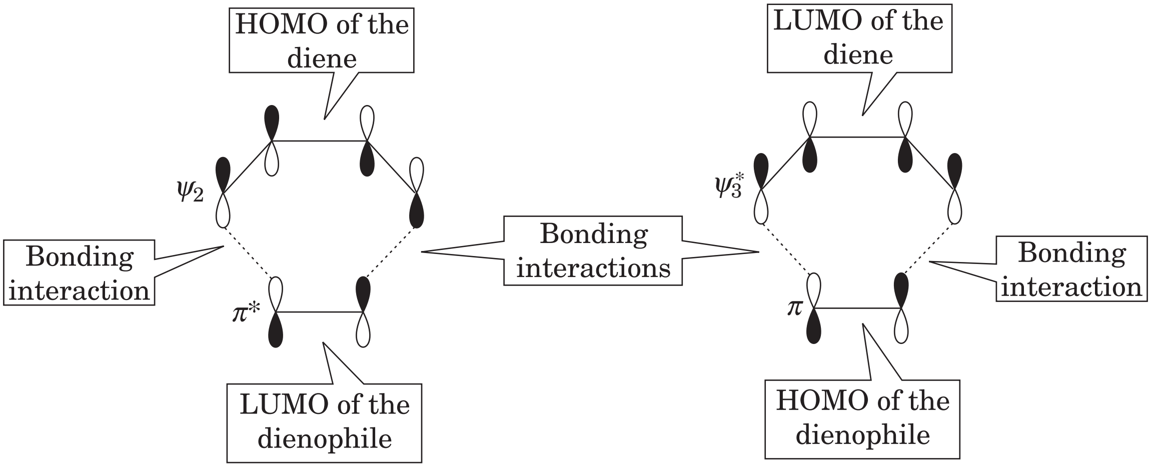
8.3.1.2 [π^4 + π^2] Cycloaddition Reactions

The [4 + 2] cycloaddition reaction between 1,3-butadiene and ethylene to form a molecule of cyclohexene (the simplest example of the Diels–Alder reaction) is thermally allowed but photochemically forbidden (i.e., unlikely to take place concertedly).



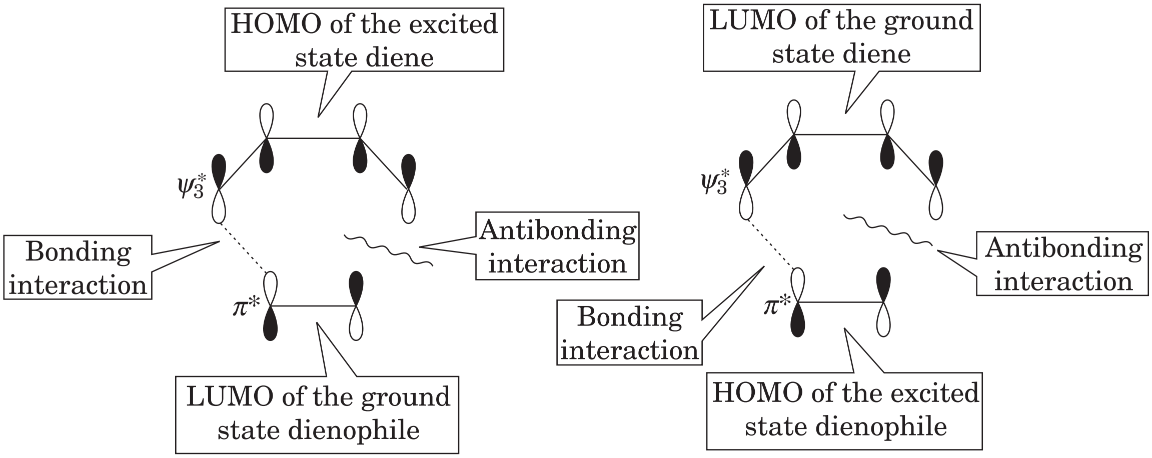
(a) Thermal reaction In this case, the HOMO of butadiene (ψ_2) interacts with the LUMO of ethylene (π^*) or the LUMO of butadiene (ψ_3^*) interacts with the HOMO of ethylene (π)

and in either case in-phase orbital overlap leading to bonding interaction takes place if the reaction is suprafacial with respect to both the components [π^4s + π^2s]. The [π^4s + π^2s] thermal cycloaddition reaction is, therefore, symmetry allowed and occurs readily through a concerted process. Although [π^2a + π^4a] mode of cyclization is symmetry allowed, it is geometrically not feasible, and so, it does not take place.



(Thermally allowed *supra–supra* mode of interaction)

(b) Photochemical reaction Under photochemical conditions, the excited state HOMO of butadiene (ψ_3^*) interacts with the ground state LUMO of ethylene (π^*) or the excited state HOMO of ethylene (π^*) interacts with the ground state LUMO of butadiene (ψ_3^*) and the processes are symmetry forbidden (i.e., they lead of antibonding interaction) if the addition is suprafacial with respect to both the components. Although the [π^4a + π^2s] and [π^4s + π^2a] mode of cycloaddition are symmetry allowed, they are geometrically very difficult and unfavourable.


HOMO of the excited state diene
ψ_3^*
Bonding interaction
π^*
Antibonding interaction
LUMO of the ground state dienophile
LUMO of the ground state diene
ψ_3^*
Antibonding interaction
Bonding interaction
π^*
HOMO of the excited state dienophile

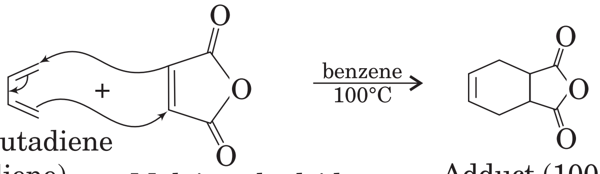
(Photochemically forbidden *supra–supra* mode of interactions)

8.3.2 Woodward and Hoffmann Selection Rules for Cycloaddition Reactions

Number of electrons	Mode of activation	Allowed stereochemical mode of the reaction
$4n$ (n = 1, 2, 3, etc.)	Thermal	supra-antara antara-supra
	Photochemical	supra-supra antara-antara
$4n + 2$ (n = 1, 2, 3, etc.)	Thermal	supra-supra antara-antara
	Photochemical	supra-antara antara-supra

8.3.3 Diels-Alder Reactions

The thermal [4 + 2] cycloaddition reaction between a conjugated diene (a 4π-electron system) and a compound containing an active multiple bond, called a dienophile (a 2π-electron system which 'loves a diene'), to form a six-membered cyclic product (often called an adduct) with one double bond is called the Diels–Alder reaction. A typical example of the Diels–Alder reaction is the reaction that occurs when 1,3-butadiene and maleic anhydride are heated together at 100°C to form the corresponding adduct in quantitative yield. We can account for all the bond changes by using curved arrows.



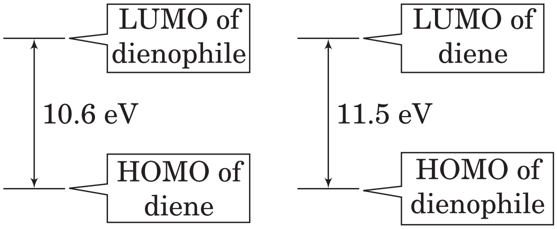
1,3-Butadiene (diene)

Maleic anhydride (dienophile)

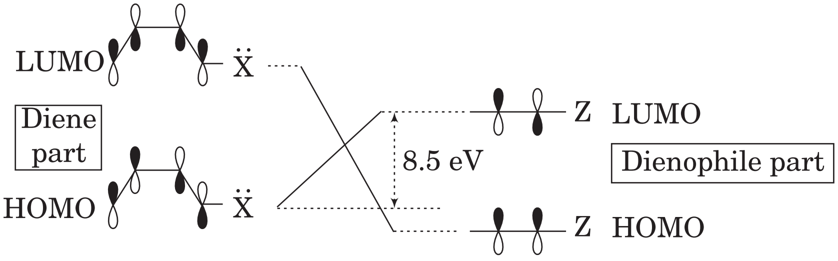
Adduct (100%)

8.3.3.1 *Reactivity of Diels–Alder Reaction*

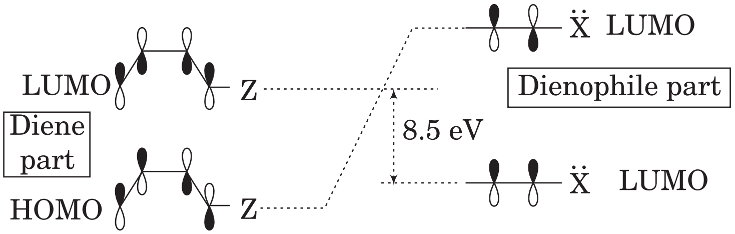
The HOMO-LUMO energy separation largely determines the reactivity or feasibility of a Diels-Alder reaction. Higher reactivity is found to be associated with a smaller energy gap between HOMO and LUMO. The value of ΔE for diene-HOMO and dienophile-LUMO is 10.6 eV and that for diene-LUMO and dienophile-HOMO is 11.5 eV. Therefore, the interaction between diene-HOMO and dienophile-LUMO is more effective for the Diels-Alder reaction.



An electron-donating group in the diene increases the energies of both HOMO and LUMO. As a consequence, the energy difference between diene-HOMO and dienophile-LUMO decreases and dienophile-HOMO and diene-LUMO increases. An electron-withdrawing group in the dienophile lowers both HOMO and LUMO energies. This also causes reduction of the energy difference between diene-HOMO and dienophile-LUMO making this HOMO-LUMO interaction clearly dominant. Therefore, an electron-donating group in diene and an electron-withdrawing group in the dienophile make the Diels-Alder reaction energetically favourable. If X is an electron-donating group at C-1 in the diene and Z is an electron-withdrawing group in the dienophile, then the energy gap between diene-HOMO and dienophile-LUMO is 8.5 eV. The energy gap is same when the diene contains an electron-withdrawing group and the dienophile contains an electron-releasing group and such Diels-Alder reactions are described as taking place with *inverse electron demand*. However, the energy separation is usually is less effective to carry out Diels-Alder reactions with inverse electron demand. It is not obvious why. When both the diene and the dienophile contains electron-donating or electron-withdrawing group, the reaction becomes less favourable energetically. The favourable HOMO–LUMO interactions are given as follows:



X = electron-donating group Z = electron-withdrawing group



Z = Electron-withdrawing group X = Electron-donating group

A conjugation extending group increases the energy of HOMO but decreases the energy of LUMO and as a consequence, the HOMO–LUMO energy gap decreases. Therefore, presence of such a group either in diene or in dienophile makes the reaction favourable.

The energy changes of HOMO and LUMO due to presence of various substituents may be summarized as follows:

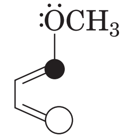
An electron-withdrawing group → slightly lowers the energy of HOMO
An electron-withdrawing group → substantially lowers the energy of LUMO

An electron-donating group → substantially raises the energy of HOMO
An electron-donating group → slightly raises the energy of LUMO

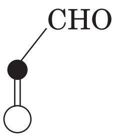
A conjugation-extending group → raises the energy of HOMO
A conjugation-extending group → lowers the energy of LUMO

8.3.3.2 Regioselectivity of Diels–Alder Reaction

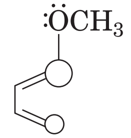
The regioselectivity of the Diels–Alder reaction depends on the coefficients of the frontier orbitals of monosubstituted diene and of the mono-substituted dienophile. The reaction of 1-methoxy-1,3-butadiene ($CH_2{=}CH{-}CH{=}CH{-}\ddot{\underset{..}{O}}CH_3$) with acrolein ($CH_2{=}CH{-}CHO$) is a regioselective one because it produces the unsaturated aldehyde I as the major product and the unsaturated aldehyde II as the minor product. The coefficients of HOMO and LUMO orbitals of 1-methoxy-1,3-butadiene (a diene with an electron-donating group) and acrolein (a dienophile with an electron-withdrawing group) can be shown as follows:



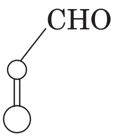
HOMO of the diene



LUMO of the dienophile

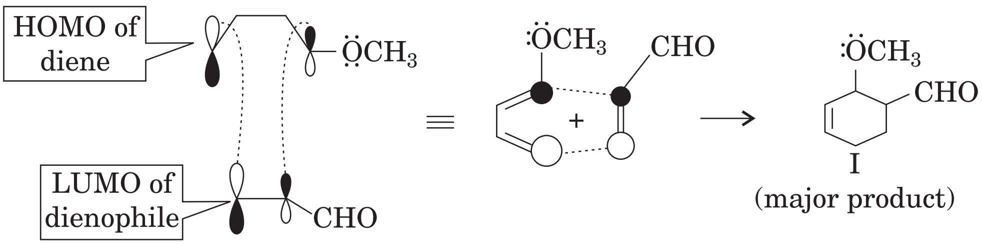


LUMO of the diene



HOMO of the dienophile

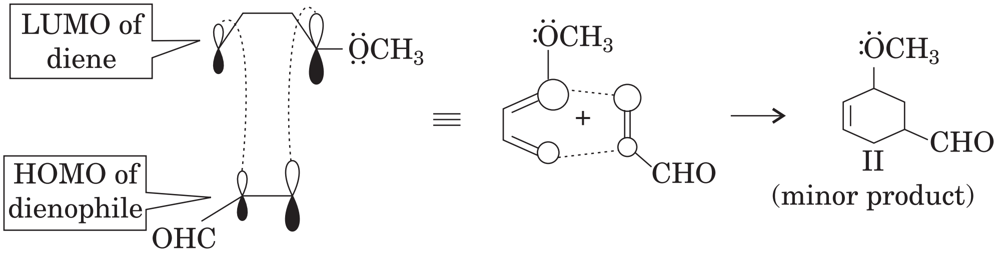
The size of each circle is roughly in proportion to the size of the coefficient of orbitals. The circles represent the lobes of p-orbitals above the plane of the paper and the shaded and unshaded one are of opposite phase sign in the usual way.



I
(major product)

$$\Delta E = E_{\text{LUMO (dienophile)}} - E_{\text{HOMO (diene)}} = 8.5 \text{ eV}$$

(large-large and small-small pairing of orbitals lead to favourable interactions)



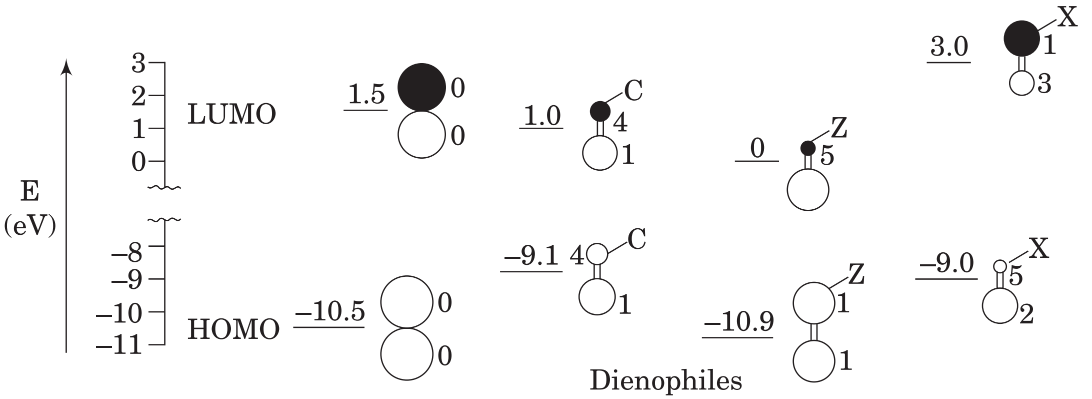
II
(minor product)

$$\Delta E = E_{\text{LUMO (diene)}} - E_{\text{HOMO (dienophile)}} = 13.4 \text{ eV}$$

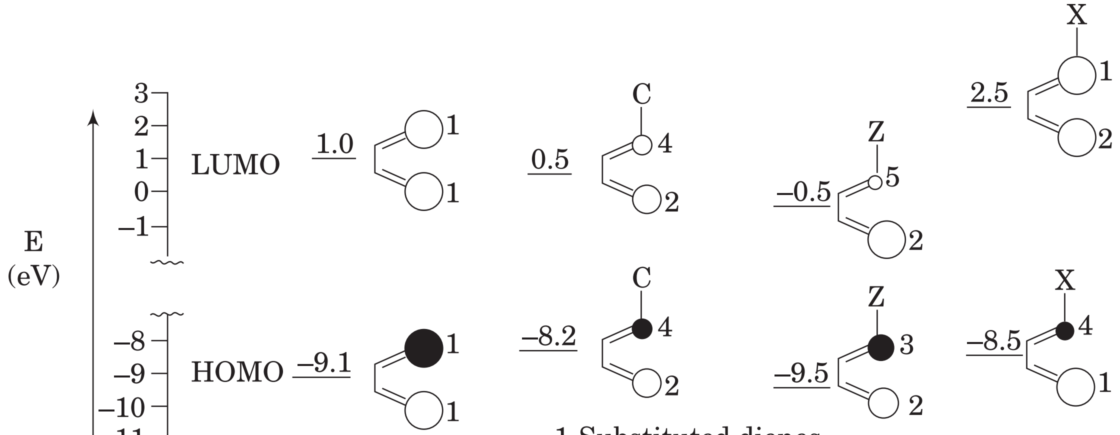
(large-large and small-small pairing of orbitals lead to favourable interactions)

Pairing of large with large (coefficients) and small with small (coefficients) takes place because this leads to greater stabilization of the system. Now, the energy difference between the diene-HOMO and dienophile-LUMO is less than that between the dienophile-HOMO and diene-LUMO. So, the former mode of interaction leads to the formation of the major product and the latter mode of interaction leads to the formation of the minor product. This explains the observed regioselectivity of the Diels-Alder reaction between 1-methoxy-1,3-butadiene and aerolein.

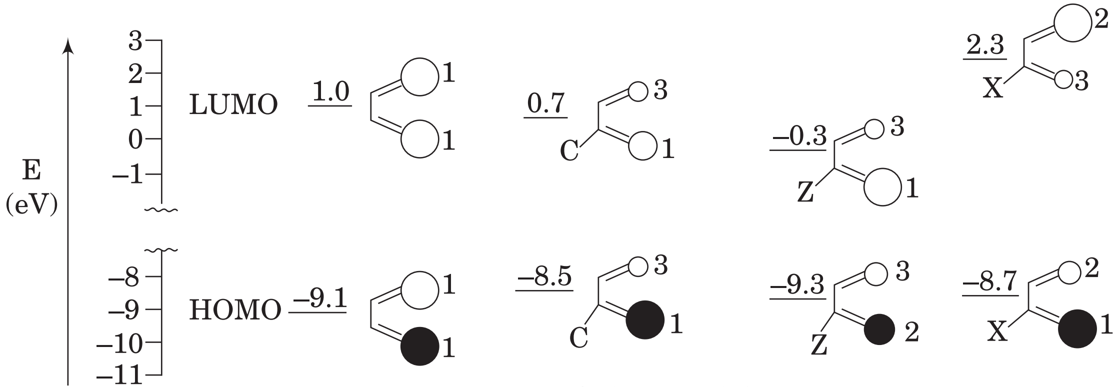
Frontier orbital energies (in eV; 1 eV = 23 kcal = 96.5 kJ) and coefficients of dienophiles (alkenes) and dienes are given as follows (C = extra conjugation, Z = electron-withdrawing group and X = electron-donating group):



Dienophiles

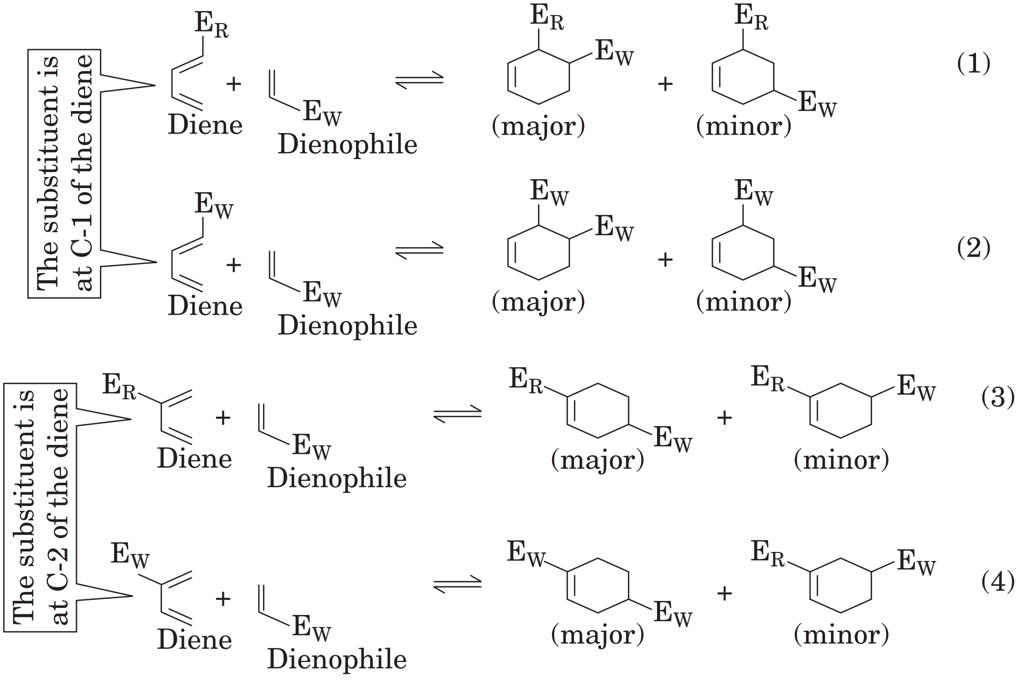


1-Substituted dienes



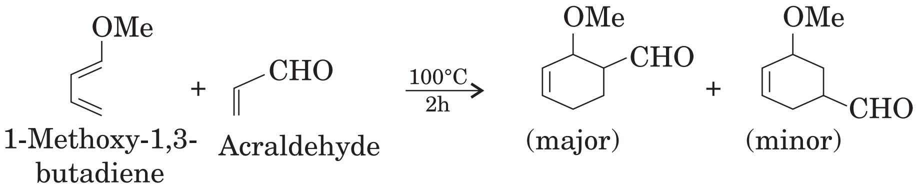
2-Substituted dienes

A schematic chart of the major and minor products in the Diels–Alder reaction is shown below:

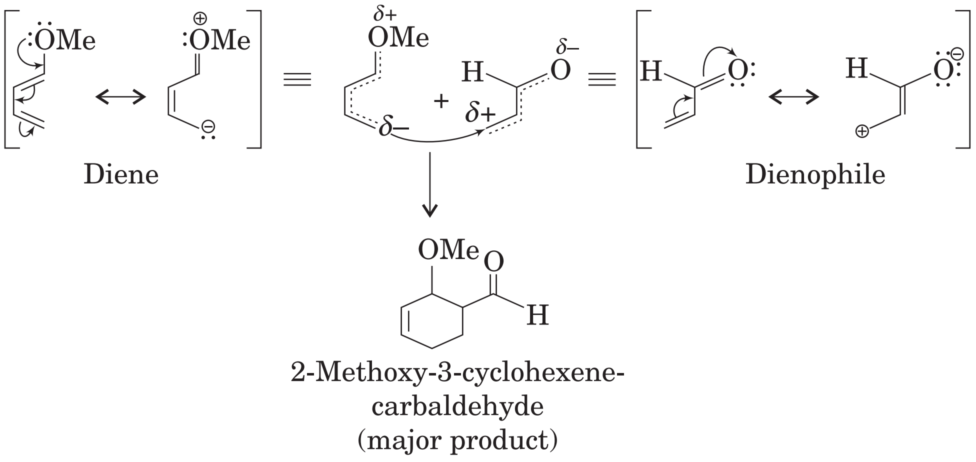

The substituent is at C-1 of the diene
The substituent is at C-2 of the diene
Diene
Dienophile
(major)
(minor)
(1)
(2)
(3)
(4)

E_R = Electron-releasing group, E_W = Electron-withdrawing group

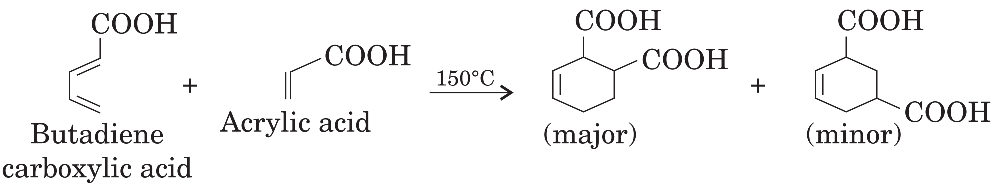
Valence bond argument of regioselectivity The regioselectivity of the reaction between 1-methoxy-1,3-butadiene and acraldehyde can be well interpreted on the basis of valence bond argument.



Which of the two isomeric products will be formed as the major product can be predicted by analysing the charge distribution in each of the reactants. Since the methoxy group (–OMe) of the diene donates electrons by +R effect, a partial negative charge is developed on the terminal carbon atom (C-4). On the other hand, the formyl group (—CHO) of the dienophile withdraw electrons by its –R effect and as a result, a partial positive charge is developed on the terminal carbon (C-3). The partially positively charged carbon of the dienophile undergoes attack preferentially by the partially negatively charged terminal carbon atom of the diene to yield 2-methyl-3-cyclohexene-carbaldehyde as the major product [equation (1)].



Although this reasoning is fine, it cannot be applied to all cases. For example, the reaction between butadienecarboxylic acid and acrylic acid is expected to yield the 'meta' adduct, whereas the reaction actually produces the 'ortho' adduct predominantly.



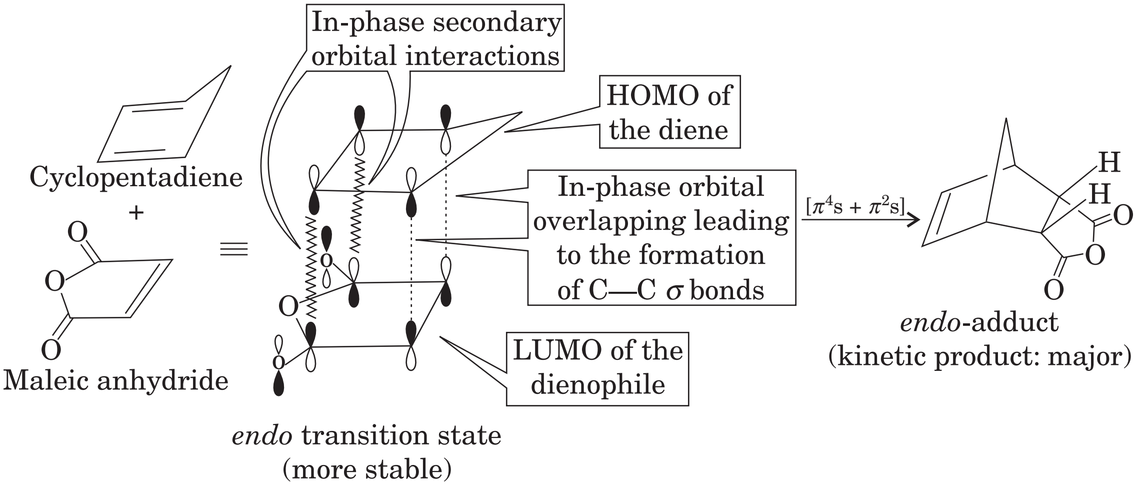
This result can, however, be explained by considering frontier orbital energies and coefficients of the diene and the dienophile [equation (2)]. The same is true for a reaction in which the electron-withdrawing group is at C-2 of the diene [equation (4)].

8.3.3.3 The Endo Rule for the Diels–Alder Reaction

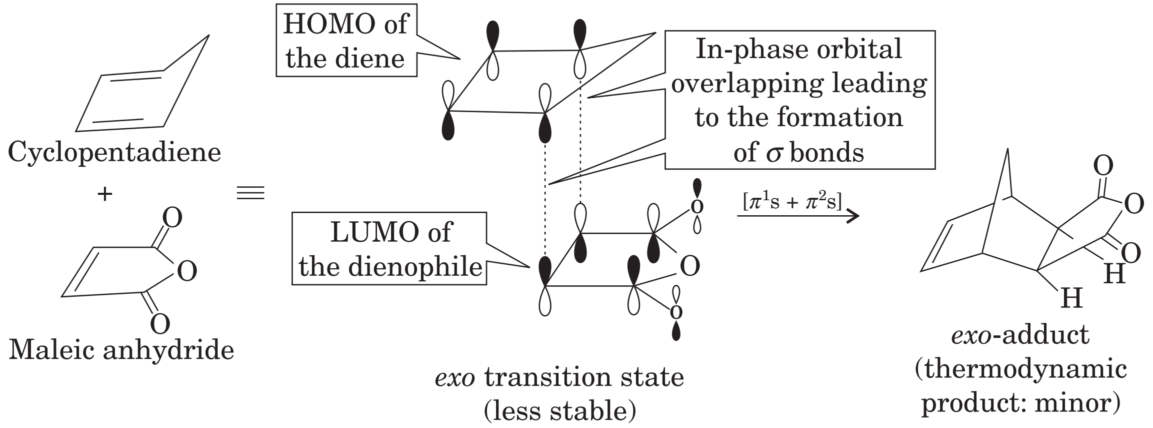
A Diels-Alder reaction prefer the *endo* product though it is sterically less stable than the *exo* (already discussed in **article no. 1.1.10.4)**. This stereochemical preference is known as the *endo rule* or *endo selectivity* and is explained by considering the secondary orbital interaction in the transition state of the reaction between the diene and the dienophile with an additional double bond ($C{=}C$ or $C{=}O$) leading to the *endo* adduct. In fact, in the *endo* transition state, there is stabilizing in-phase secondary orbital interactions between the *p*-orbitals of the LUMO of the electron acceptor substituent and the *p*-orbitals of the developing pi bond at the back of HOMO of the electron-rich diene. This stabilizing interaction (although not bond forming because the distance between two orbitals is greater than that required for effective overlap leading to a σ bond) makes the *endo* transition state considerably stable and for this, the *endo* adduct is formed predominantly. On the other hand, the formation of the *exo* adduct involves a higher energy transition state because it is not assisted by any secondary orbital interactions. Therefore, the *exo* adduct becomes the minor product. Actually the *endo* adduct is the kinetic product formed at a lower temperature, whereas the *exo* adduct is the thermodynamic product formed predominantly at a higher temperature. In fact, at higher temperature, when an equilibrium is reached, the initially formed *endo*-adduct (the kinetic product) dissociates by a retro Diels–Alder reaction denoted as $[\pi^2 s + \sigma^2 s + \sigma^2 s]$ and the components then react to give the *exo*-adduct (the thermodynamic product) predominantly. Thermal reversion of an allowed cycloaddition must also be allowed, since both the reactions proceed through the same reaction path and have same transition state (principle of microscopic reversibility).

The symmetry-allowed $[\pi^4 s + \pi^2 s]$ cycloaddition reaction between cyclopentadiene and maleic anhydride leading to formation of *endo*-adduct (major) and *exo*-adduct (minor) is shown below:

***endo*-Approach:**

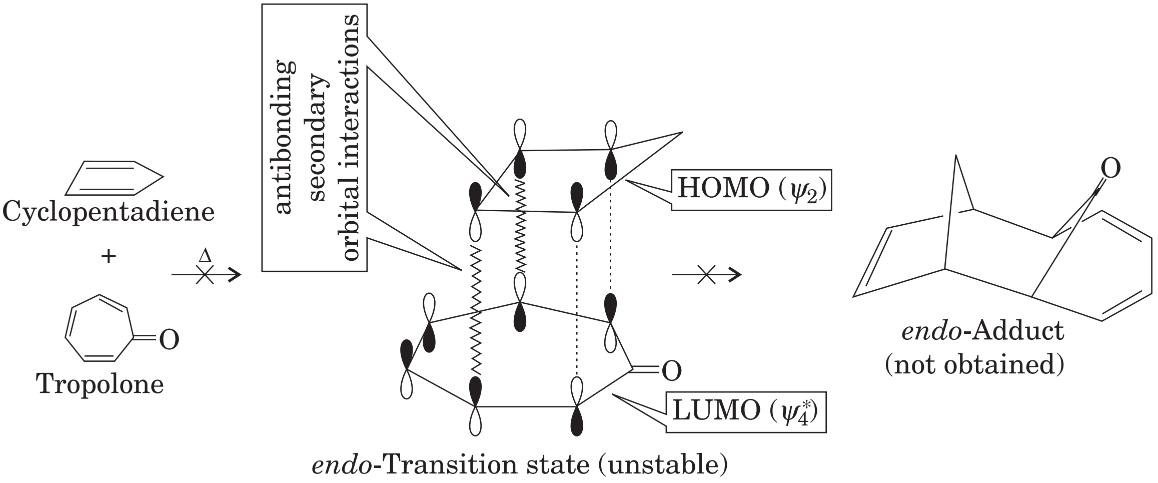

In-phase secondary orbital interactions
HOMO of the diene
Cyclopentadiene
+
O
O
O
Maleic anhydride
≡
O
O
O
In-phase orbital overlapping leading to the formation of C—C σ bonds
LUMO of the dienophile
endo transition state (more stable)
[π⁴s + π²s]
H
H
O
O
O
endo-adduct (kinetic product: major)

***exo*-Approach:**

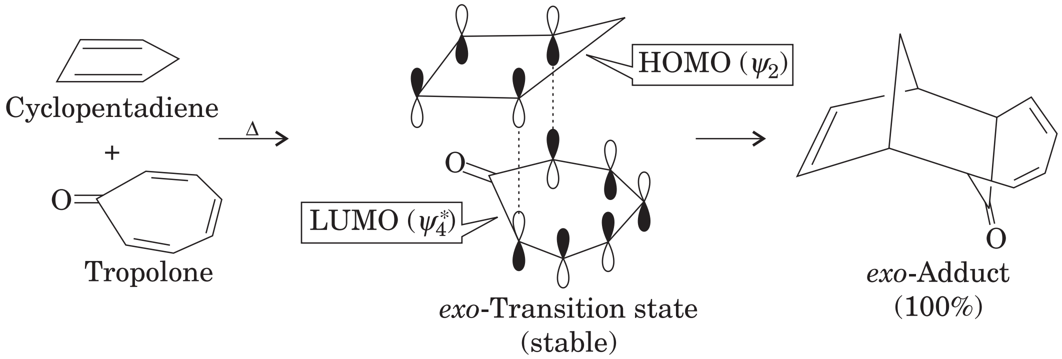

Cyclopentadiene
+
Maleic anhydride
≡
HOMO of the diene
In-phase orbital overlapping leading to the formation of σ bonds
LUMO of the dienophile
[π¹s + π²s]
exo transition state (less stable)
exo-adduct (thermodynamic product: minor)
O
H

Exception to the *endo*-rule It is not true that always the *endo*-addition will be preferred kinetically. There are a few cases where *exo*-adduct predominates over the *endo*-adduct at lower temperature and this is because in such cases, the stabilizing out-of-phase secondary orbital interactions make the *endo* transition state relatively less stable. For example, in the cycloaddition reaction between cyclopentadiene and tropolone, the two stereo orientations (*endo* and *exo*) are possible for the allowed [π^6s + π^4s] mode of cycloaddition. However, the reaction leads to the formation of the *exo*-adduct at lower temperature. This is because the secondary orbital interactions in the *endo* transition state are out-of-phase orbital interactions which highly destabilize the transition state.

***endo*-Approach:**

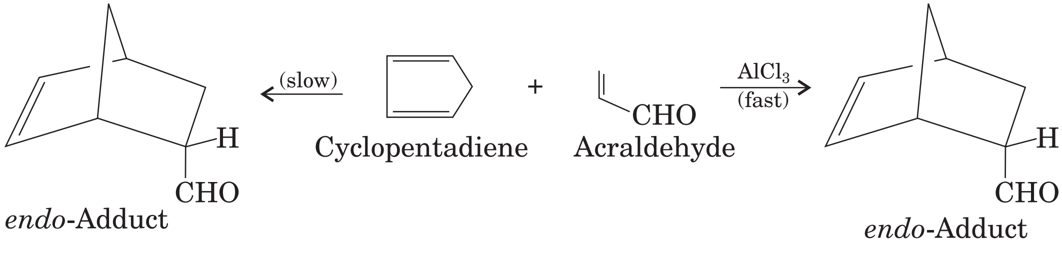

antibonding secondary orbital interactions
Cyclopentadiene
+
Tropolone
Δ
HOMO (ψ₂)
LUMO (ψ₄*)
O
endo-Adduct (not obtained)
endo-Transition state (unstable)

***exo*-Approach:**

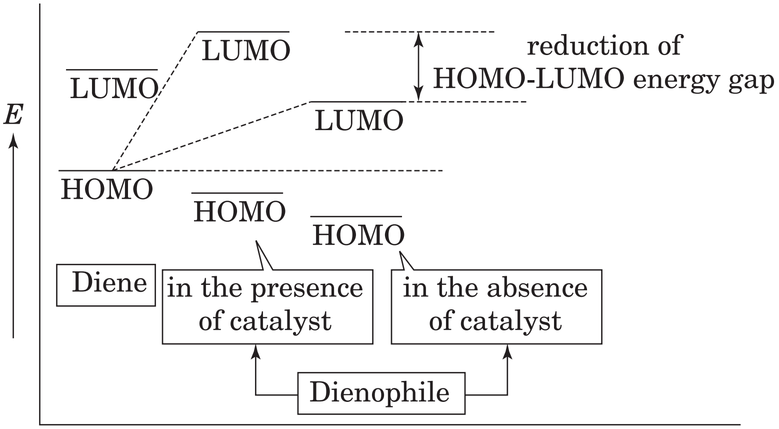


8.3.3.4 *Effect of Lewis Acids on Diels–Alder Reactions*

Lewis acids exert a strong catalyzing effect on Diels-Alder reactions. The influence of Lewis acid on the rate of Diels-Alder reactions may be ratioalised by FMO approach. It is known that the smaller the energy difference between the HOMO of the diene and the LUMO of the dienophile, the more readily the reaction occurs because in that case overlapping becomes better. Coordination of a Lewis acid with the non-bonding electrons of a carbonyl $(\rangle C{=}\ddot{O}{:})$ or a cyano $(—C\equiv\ddot{N})$ group present in the dienophile lowers the energies of the FMOs of the dienophile and alters the distribution of the coefficients of the atomic orbitals. Due to decrease of FMO energies, the energy difference between the HOMO of the diene and the LUMO of the dienophile reduces while the energy difference between the HOMO of the dienophile and the LUMO of the diene increases. Thus, the former FMOs interacts at a faster rate to give the adduct through a low energy transition state. Finally, the increased LUMO coefficient (larger size of the *p*-orbital on the carbonyl carbon) causes more effective secondary orbital interaction than in the case of uncatalysed reaction and accounts for greater *endo* selectivity. For example:

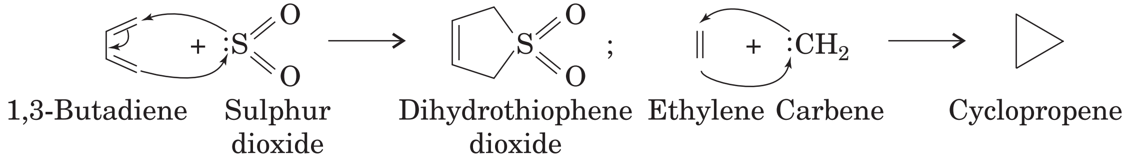


The relative frontier orbital energies of the diene and catalysed/uncatalysed dienophile and the reduction of HOMO-LUMO energy gap is shown in the following diagram:

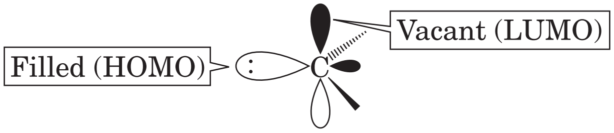


8.3.3.5 Cheletropic Reactions

Cheletropic reactions are a kind of concerted cycloadditions or cycloreversions in which the two σ bonds are made or broken to the same atom. The species which reacts through a single atom possesses both a filled and a vacant orbital. Molecules like singlet $:SO_2$, singlet $:CH_2$ etc. possess a filled as well as a vacant orbital on the same atom (here S and C). Addition of SO_2 to diene and of carbenes to alkenes are two well-known examples of cheletropic reaction:

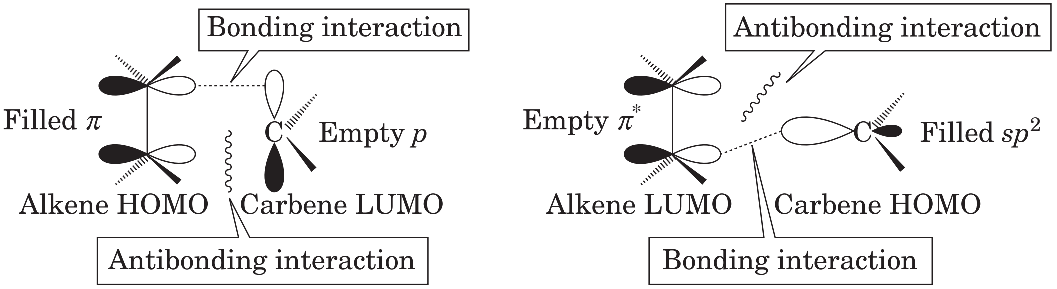


Let us consider the HOMO–LUMO interactions of the reacting species involved in the second reaction leading to the formation of cyclopropane. There are two possibilities in which the carbene ($:CH_2$) can approach the olefin: *linear* and *non-linear*. Carbene has two π-MOs, HOMO containing both the electrons and LUMO which is vacant.



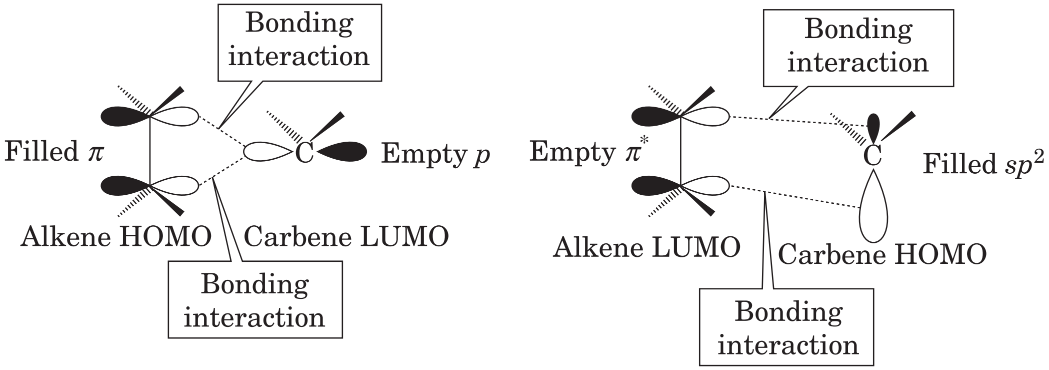
Orbital structure of a singlet carbene

The linear approach of the carbene can be represented as shown below. In this case, the plane of the bonds of the two substituents on carbene is perpendicular to that of the C—C bond of the alkene.



(Linear approach of carbene to an alkene)

From the above figure it becomes clear that the linear approach of the carbene to the alkene is impossible to build two new bonds because there is always an antibonding interaction. Two new bonds can be formed, however, if the carbene approaches the alkene in non-linear manner. In the non-linear approach of carbene, as shown below, the plane of the bonds of the two substituents on carbene is parallel to that of the C—C bond of the π-system.



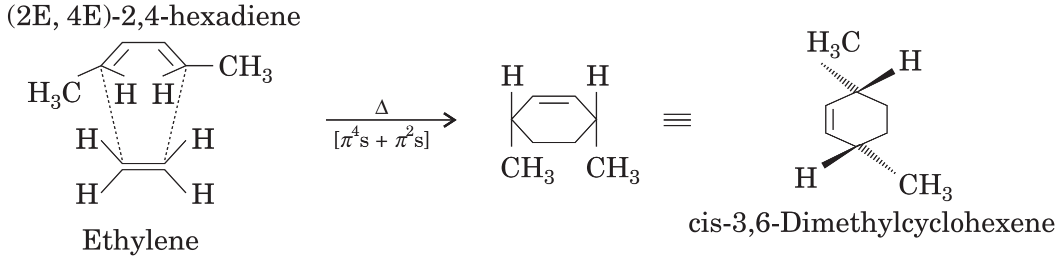
(Non-linear approach of carbene to an alkene)

SOLVED PROBLEMS

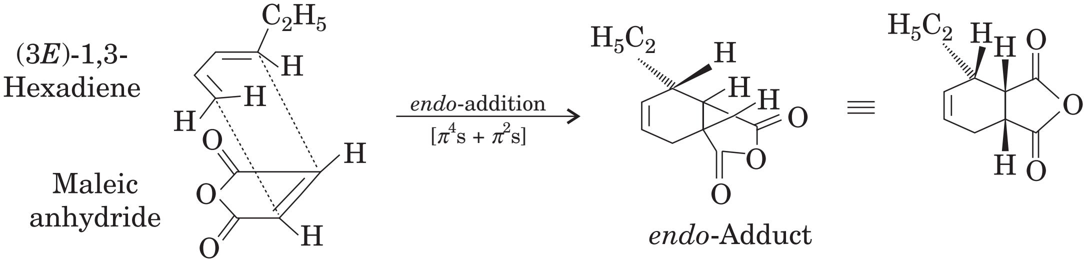
1. **Predict the product expected to be formed in each of the following reactions and explain its formation:**
   - **(a) (2*E*, 4*E*)-2,4-hexadiene + ethylene** $\xrightarrow{\Delta}$
   - **(b) (3*E*)-1,3-hexadiene + maleic anhydride** $\xrightarrow{\Delta}$
   - **(c) (*Z*)-2-butene** $\xrightarrow{h\nu}$
   - **(d) (*E*)-2-butene + (*Z*)-2-butene** $\xrightarrow{h\nu}$

Solution

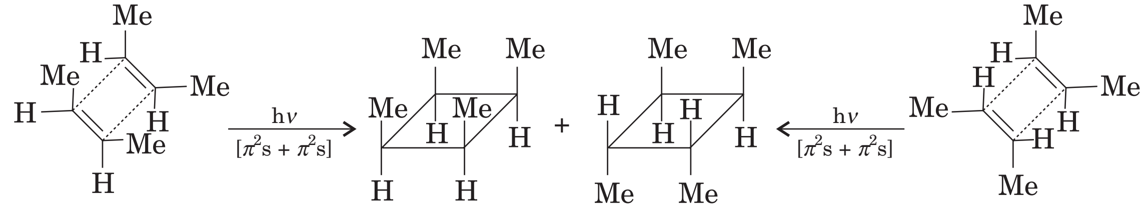
(a) This is a thermal [4 + 2] cycloaddition reaction, i.e., it is an example of the familiar Diels-Alder reaction. The *supra-supra* fashion of addition is symmetry-allowed and also geometrically facile. Since the addition is *syn*, the two outer methyl group must have a *cis* relationship in the product. Placing the diene in the required *s-cis* conformation we may get the product as follows:



(b) This is also a thermal [4 + 2] cycloaddition reaction which occurs by a symmetry-allowed *supra–supra* fashion. Since the dienophile maleic anhydride is a *cis*-alkene and the Diels-Alder reaction is a *syn*-addition, the stereochemistry of the junction is *cis*, i.e., it is *cis*-fused. The addition occurs in the energetically favourable *endo* fashion to give the product in which the ethyl group is *cis* to the anhydride bridge.

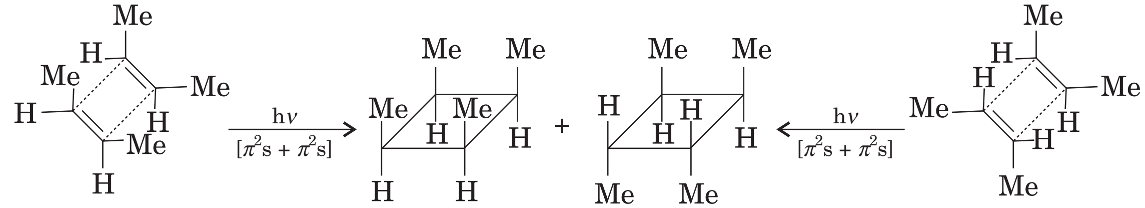


(c) This is a photochemical [2 + 2] cycloaddition which takes place by a symmetry-allowed *supra–supra* mode of interaction. This causes *syn*-addition to each alkene and as a consequence, the two methyl groups of each alkene unit remains *cis* to each other in the product. The two alkene units may combine in two fashions to give two diastereoisomeric tetramethylcyclobutanes.

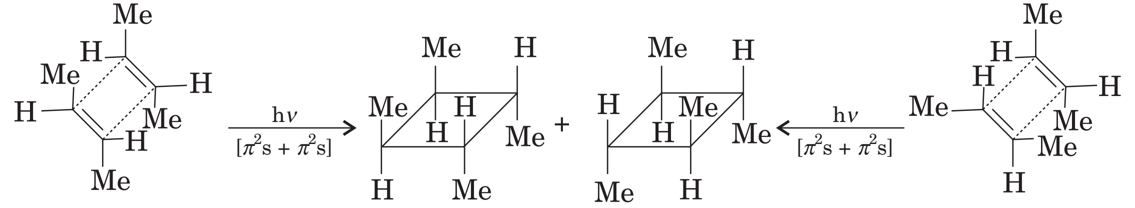


(*Z*)-2-Butene (two molecules) I II (*Z*)-2-Butene (two molecules)

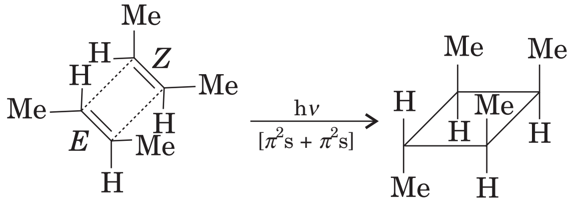
(d) This symmetry-allowed photochemical [2 + 2] cycloaddition leads to the formation of four (I–IV) diastereoisomeric tetramethylcyclobutane. The two methyl groups of each alkene unit will remain *cis* to each other in the product.



(*Z*)-2-Butene (2 molecules) I II (*Z*)-2-Butene (2 molecules)



(*E*)-2-Butene (2 molecules) II III (*E*)-2-Butene (2 molecules)



(*E*)-2-Butene + (*Z*)-2-Butene IV

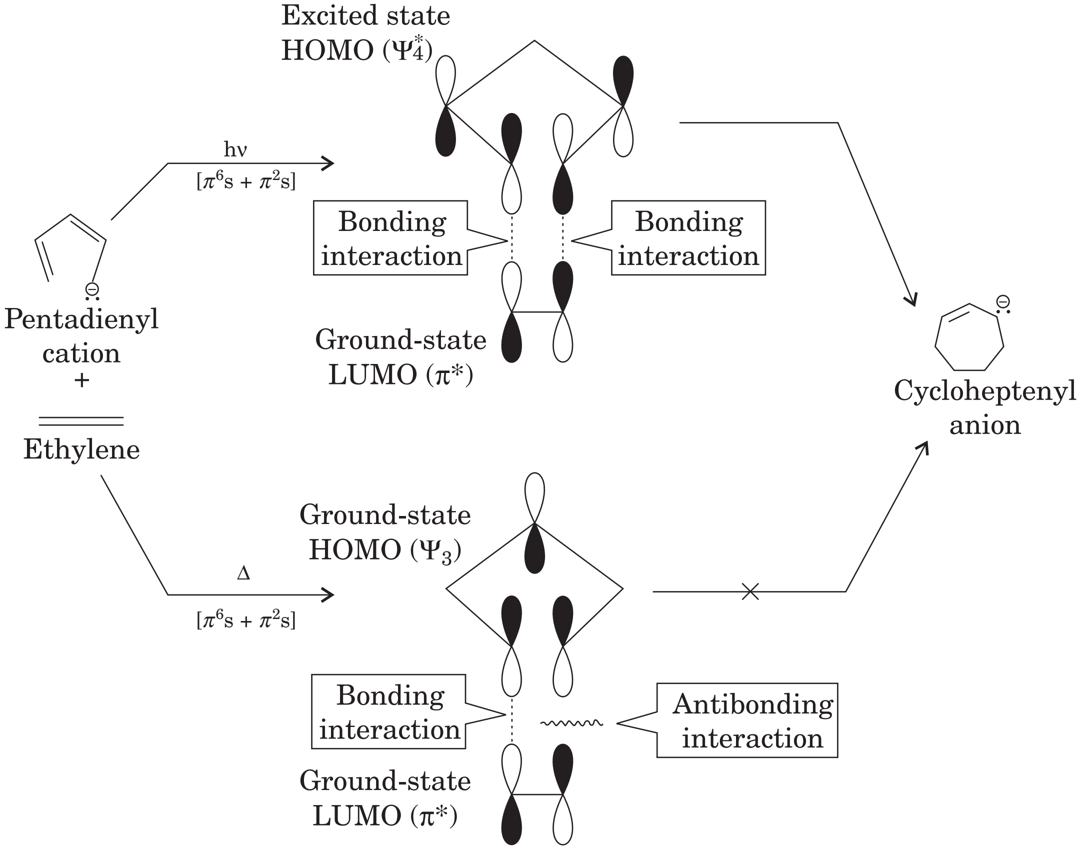
2. Determine whether the following *supra–supra* mode of cycloaddition reactions are symmetry-allowed thermally or photochemically?

(a) Pentadienyl anion + ethylene → cycloheptenyl anion

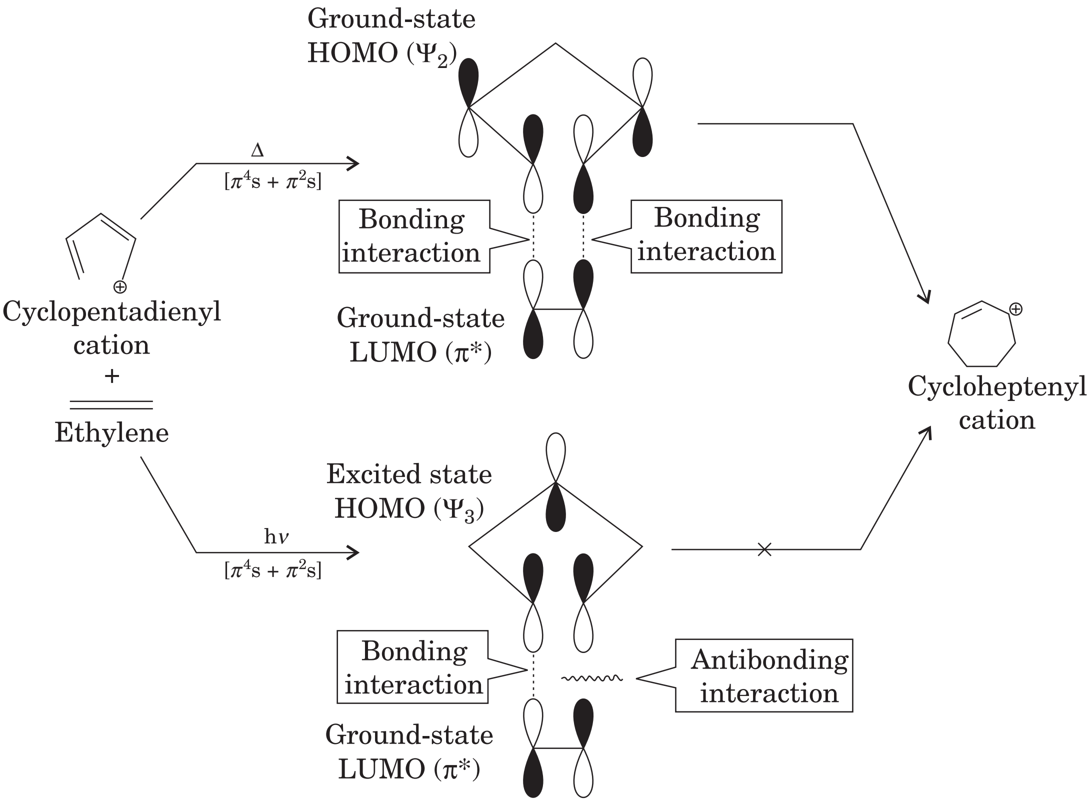
(b) Pentadienyl cation + ethylene → cycloheptenyl cation

Solution

(a) It is a $[\pi^6 s + \pi^2 s]$ process and is, therefore, symmetry allowed under photochemical condition but symmetry forbidden under thermal condition.

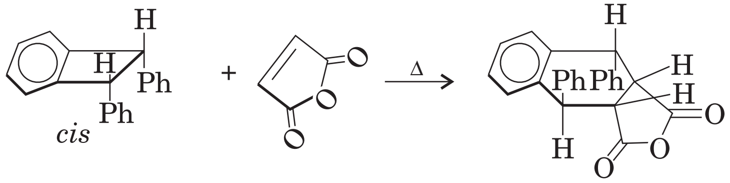


(b) It is a $[\pi^4 s + \pi^2 s]$ process and is, therefore, symmetry allowed under thermal condition but symmetry forbidden under photochemical condition.



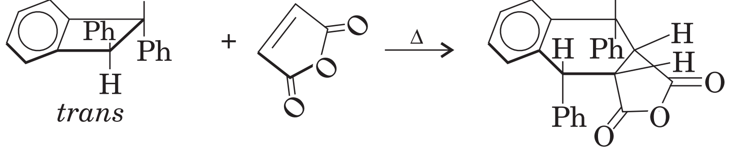
3. Explain the formation of the product obtained in each of the following reactions:

(a)



I

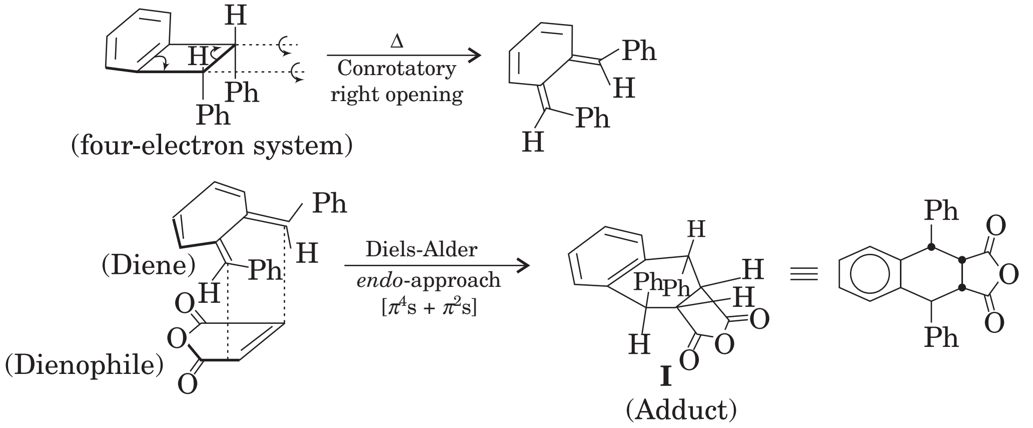
(b)



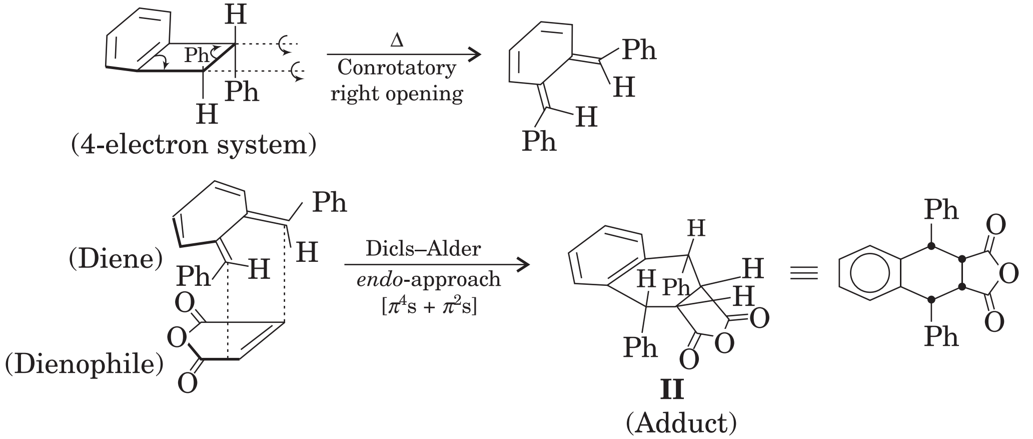
II

Solution In each of these two pericyclic reactions, a conrotatory ring opening of the cyclobutene ring (a four-electron system) first takes place to form a non-aromatic intermediate which may act as a diene in the Diels–Alder reaction. This intermediate then readily undergoes a Diels–Alder reaction with maleic anhydride through [$\pi^4s + \pi^2s$] mode and by *endo* fashion to yield the aromatic product (I or II).

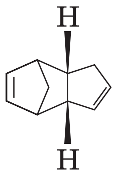
(a)



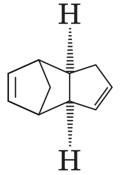
(b)



4. **Cyclopentadiene spontaneously dimerizes at room temperature to form *endo*-dicyclopentadiene (I) rather than its *exo*-isomer (II). Again, when the dimer is heated under a fractionating column cyclopentadiene is regenerated. Explain these observations.**



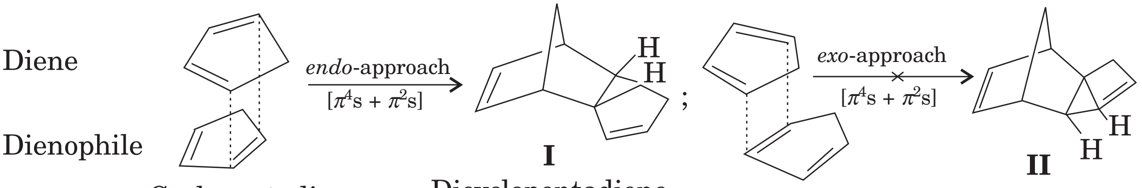
I



II

Solution When one molecule of cyclopentadiene acts as a diene and the other molecule acts as a dienophile in a Diels–Alder reaction, dicyclopentadiene is formed by a [$\pi^4s + \pi^2s$]

process. The reaction may take place through the following two different stereochemical approaches to give the *endo*-isomer of dicyclopentadiene (I) and the *exo*-isomer (II). However, only I is obtained.

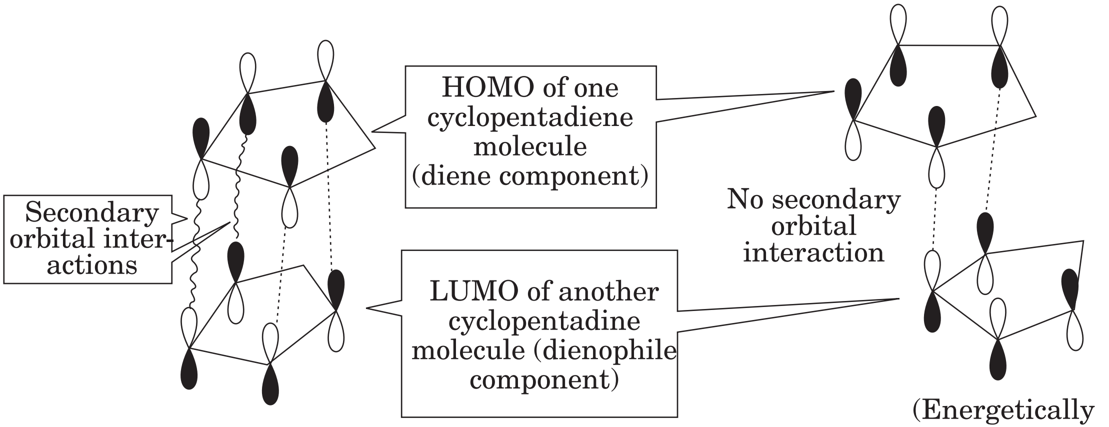


Cyclopentadiene (two molecules)

I Dicyclopentadiene (*endo*-isomer)

II Dicyclopentadiene (*exo*-isomer)

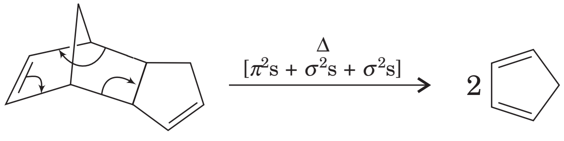
FMO interactions:


HOMO of one cyclopentadiene molecule (diene component)
Secondary orbital interactions
No secondary orbital interaction
LUMO of another cyclopentadine molecule (dienophile component)

(Energetically more favourable *endo*-approach)

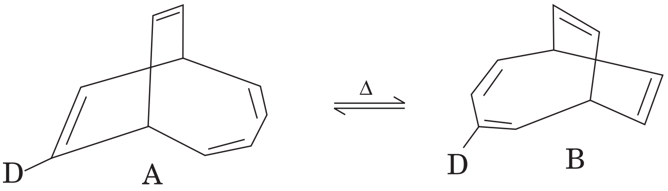
(Energetically less favourable *exo*-approach)

When dicyclopentadiene is heated under a fractionating column, it regenerates cyclopentadiene by a *retro*-Diels–Alder reaction with the equilibrium being shifted to replace the more volatile cyclopentadiene which is being removed by distillation.

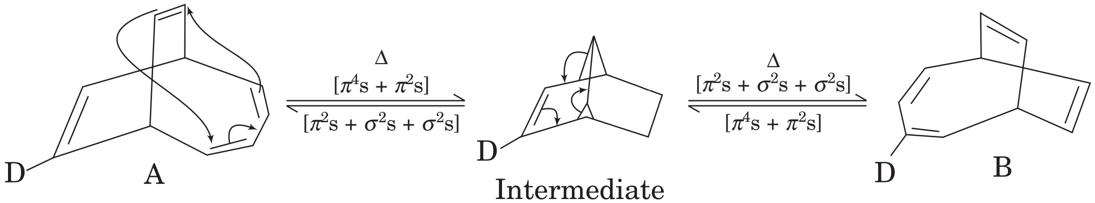


Dicyclopentadiene Cyclopentadiene

5. **Account for the following observation related to scambling of deuterium between A and B:**



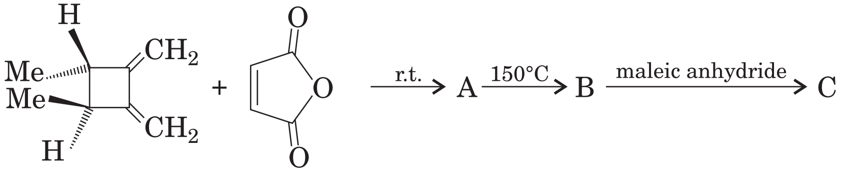
Solution The scambling of deuterium between A and B can be explained on the basis of an intramolecular Diels–Alder reaction followed by a *retro*-Diels–Alder reaction. This transformation may be shown as follows:


D
A
Δ
[π^4s + π^2s]
[π^2s + σ^2s + σ^2s]
D
Δ
[π^2s + σ^2s + σ^2s]
[π^4s + π^2s]
D
B

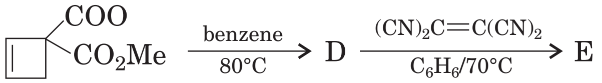
Intermediate

6. **Identify the product obtained in each step of the following reaction sequences and account for its formation:**

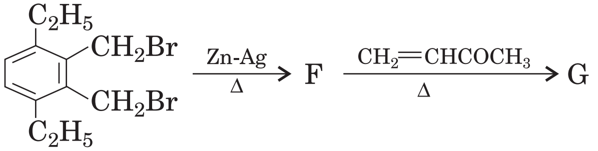
(a)



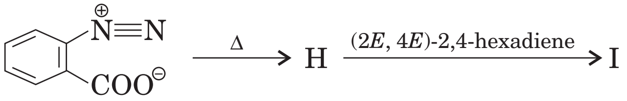
(b)



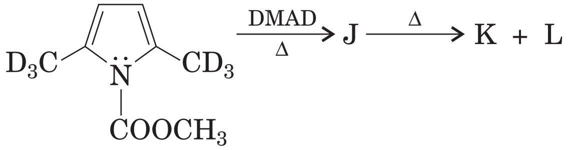
(c)



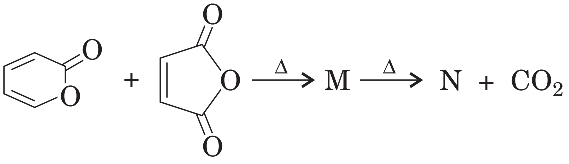
(d)



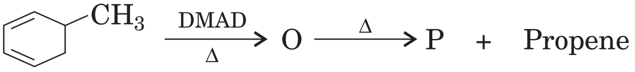
(e)



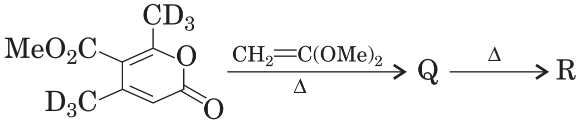
(f)



(g)

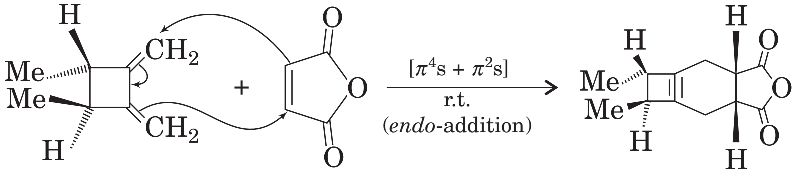


(h)



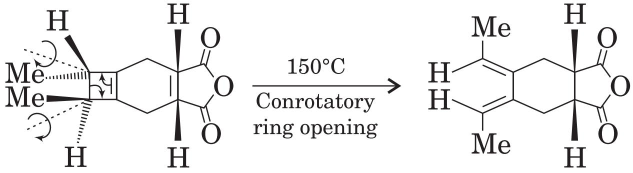
Solution

(a) In the first step of this reaction sequence is a [π^4s + π^2s] thermal cycloaddition (a Diels–Alder reaction) to yield the compound A.



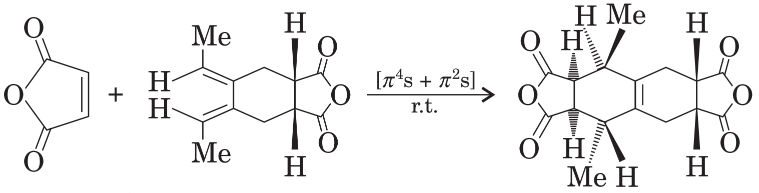
(Diene) (Dienophile) (adduct) A

In the second step, a symmetry-allowed thermal cycloreversion occurs in conrotatory fashion to give the compound B.



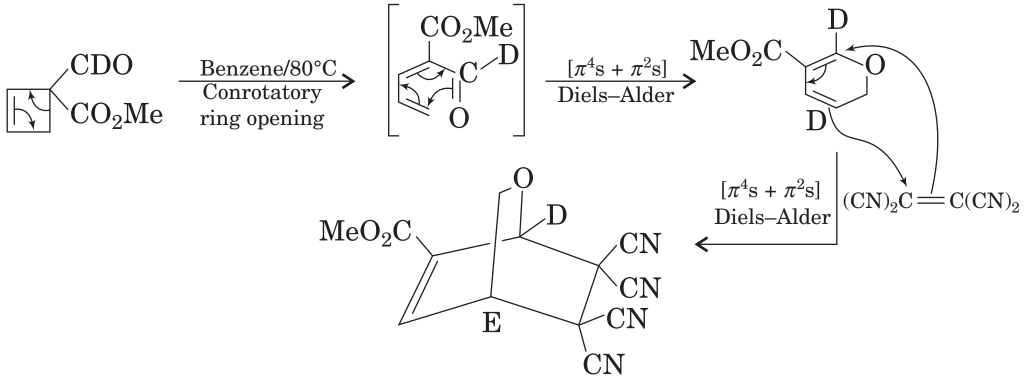
B

In the third step, the compound B undergoes a [π^4s + π^2s] cycloaddition reaction with maleic anhydride through *endo*-fashion to yield the compound C.

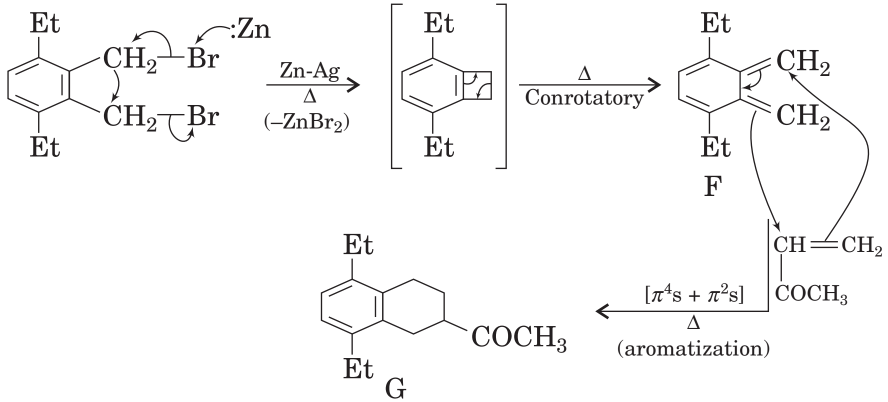


(Dienophile) (Diene) (adduct) C

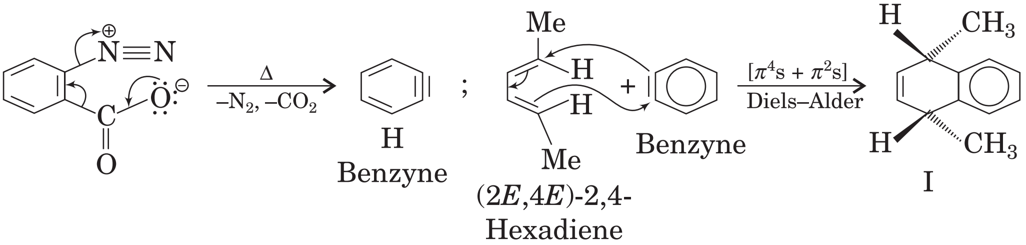
(b) The cyclobutene ring (a 4n electron system, where n = 1) undergoes a thermal conrotatory ring opening to yield an unsaturated aldehyde which undergoes a ready intramolecular [4 + 2] cycloaddition reaction (the C=O function acts as a dienophile) to give the diene D. In the next step, a [π^4s + π^2s] addition occurs between D and tetracyanoethylene to give the adduct E.



(c) The starting dibromide undergoes debromination by metallic zinc with simultaneous ring closure to give a strained cyclobutene system which undergoes ready conrotatory ring opening to yield the diene F. In the next step, this diene reacts with the dienophile to give the adduct G through a [π^4s + π^2s] process.

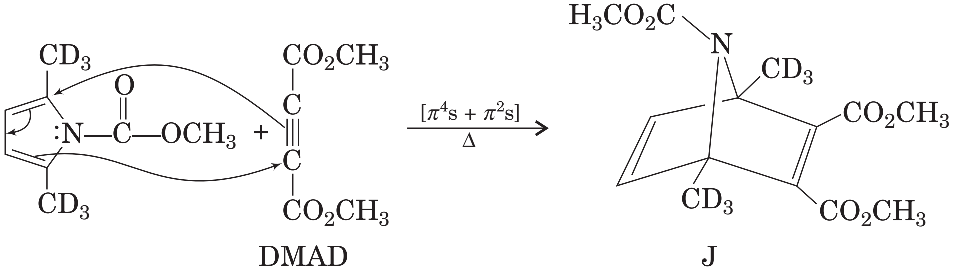


(d) When the starting zwitterion is heated, it undergoes elimination of CO_2 and N_2 to yield benzyne (H). In the next step, benzyne undergoes a [π^4s + π^2s] addition reaction with (2*E*, 4*E*)-2,4-hexadiene to produce the compound I in which the two outer methyl groups are *cis*- to each other.

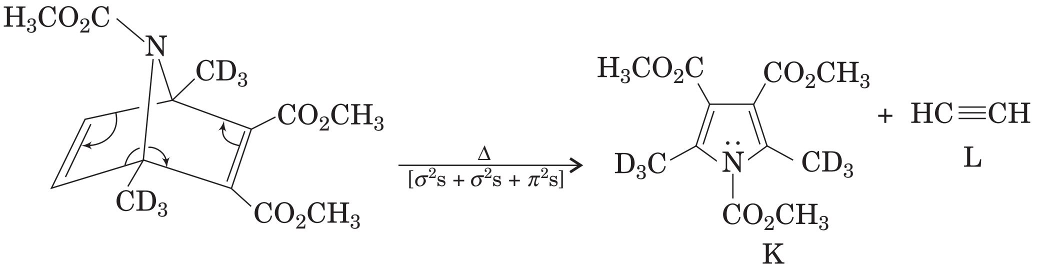


(e) Due to presence of the electron-withdrawing —$COOCH_3$ group on nitrogen, the electron availability on nitrogen is reduced and the pyrrole derivative can then act as a diene in a Diels–Alder reaction with DMAD, the dienophile.

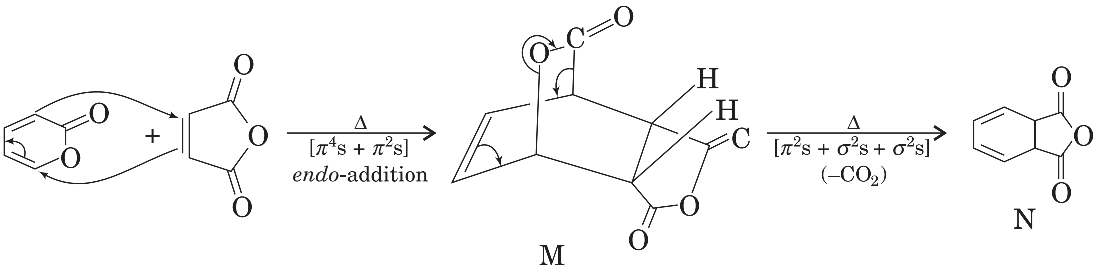
The first step is, therefore, a [4 + 2] cycloaddition reaction that occurs in *supra-supra* fashion to give the adduct J.



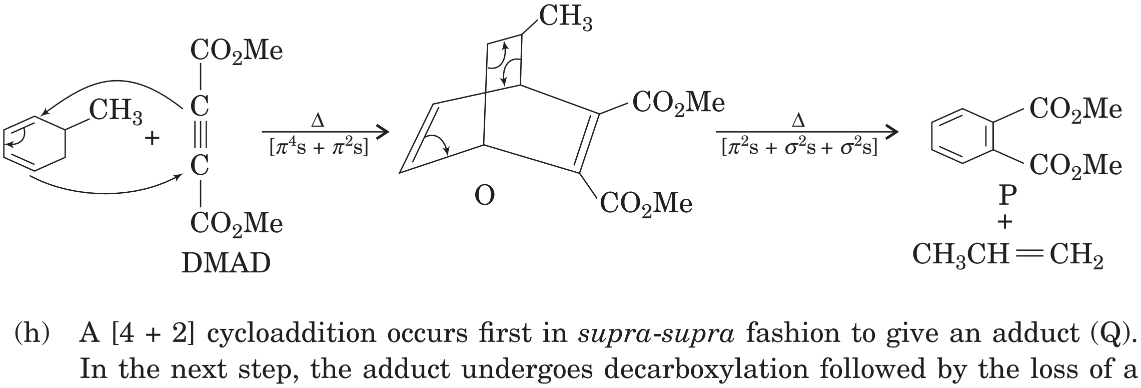
In the second step, the adduct J undergoes a $[\pi^2s + \sigma^2s + \sigma^2s]$ cycloreversion (*retro*-Diels–Alder reaction). Irreversible loss of gaseous acetylene drives the reaction towards the product.



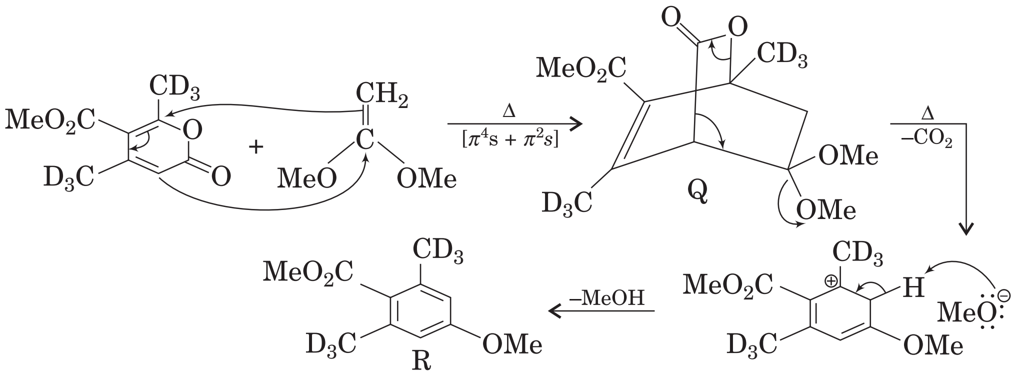
(f) In the first step, a $[\pi^4s + \pi^2s]$ cycloaddition reaction occurs in *endo*-fashion to yield the adduct M. In the next step, the adduct undergoes decarboxylation (a *retro*-Diels–Alder reaction) to give the product N.



(g) A [4 + 2] cycloaddition followed by cycloreversion leads to the formation of compounds O and P, respectively.

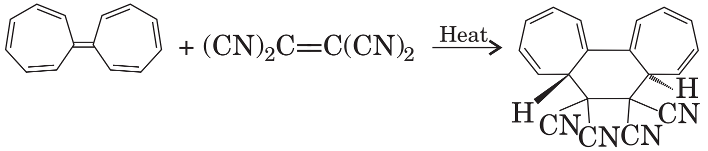


(h) A [4 + 2] cycloaddition occurs first in *supra-supra* fashion to give an adduct (Q). In the next step, the adduct undergoes decarboxylation followed by the loss of a molecule of methanol to yield the benzene derivative R.

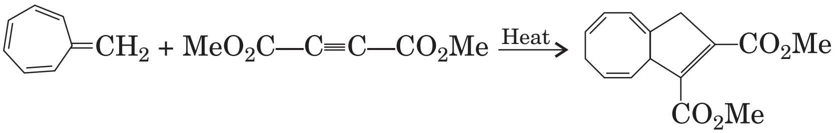


7. Explain the following cycloaddition reactions:

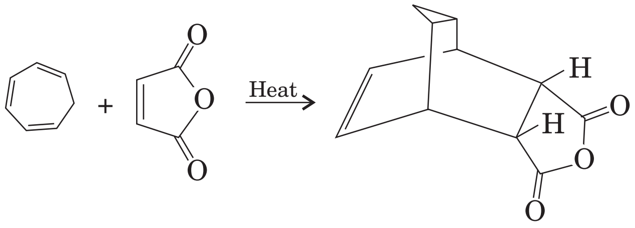
(a)



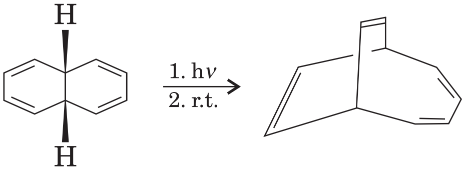
(b)



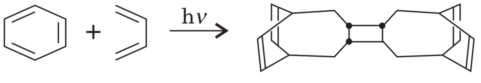
(c)



(d)



(e)



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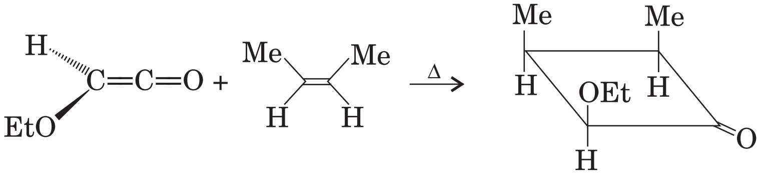
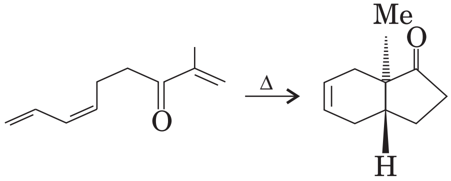
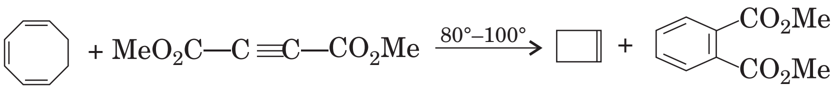


(g)

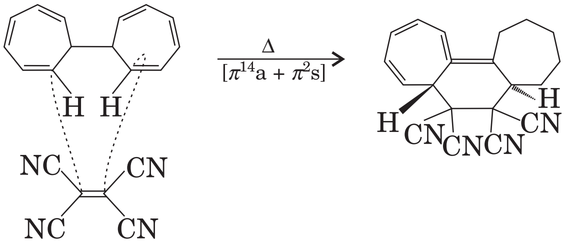


(h)

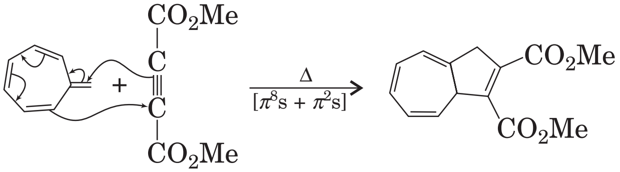


Solution

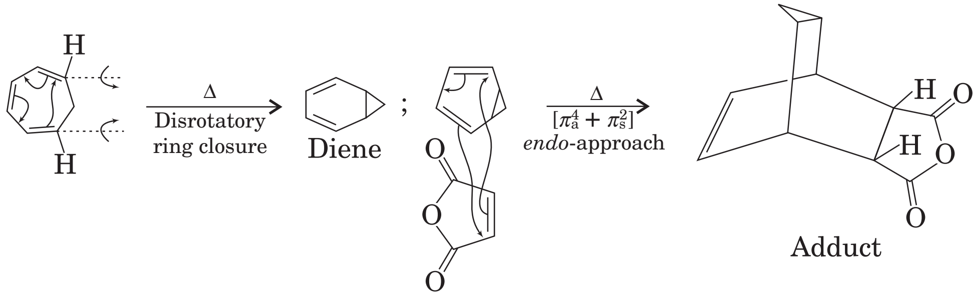
(a) This is a [14 + 2] cycloaddition reaction which is thermally allowed in *antara*, *supra* or *supra*, *antara* mode. However, the [π^{14}a] + π^2s] process is more likely than the alternative [π^{14}s + π^2a] mode. The antarafacil addition on the heptafulvene molecule is possible because its twisted shape does not destabilise the transition state much.



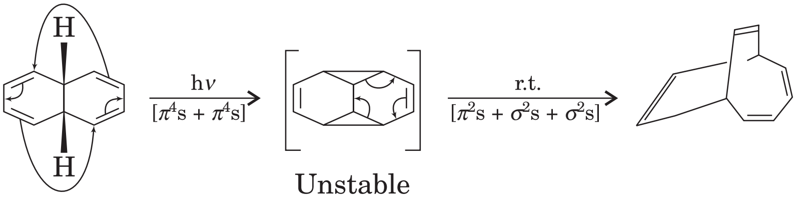
(b) This [8 + 2] thermal cycloaddition reaction takes place in geometrically feasible *supra*, *supra* fashion to yield a bicyclic product.



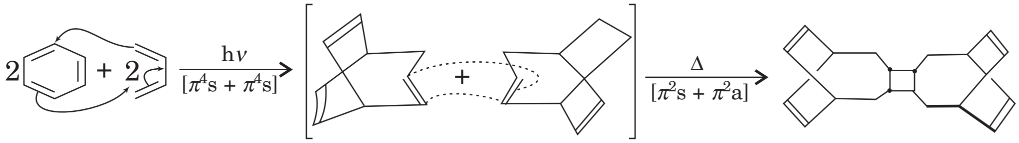
(c) This triene being a 6π-electron system undergoes disrotatory ring closure to give a diene which then undergoes a [π^4s + π^2s] cycloaddition reaction with maleic anhydride in endo fashion to give the corresponding adduct.



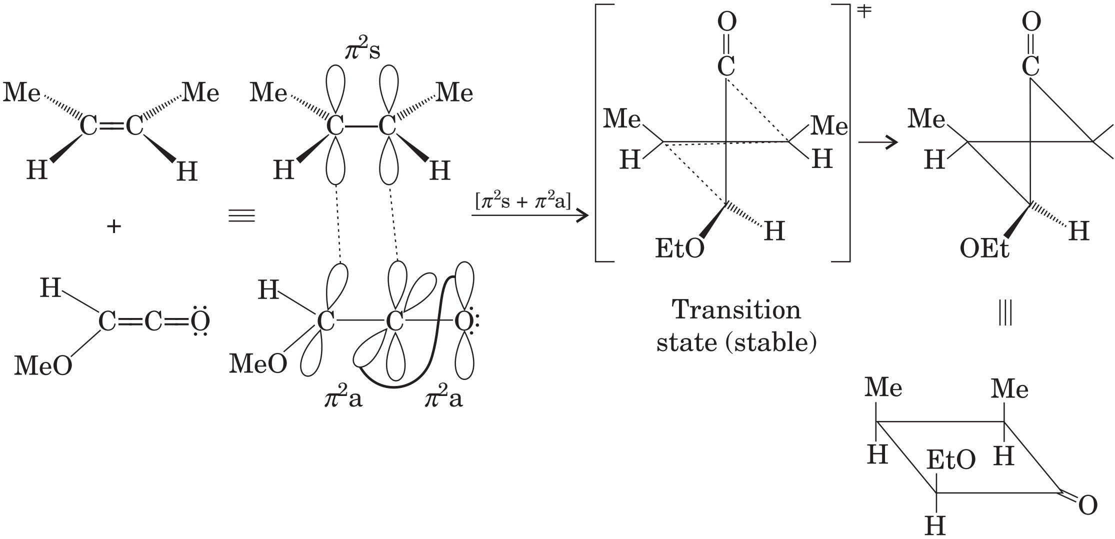
(d) The compound undergoes an intramolecular [4 + 4] photochemical cycloaddition in symmetry allowed *supra*, *supra* fashion. The resulting unstable compound undergoes ready [4 + 2] cyclo-reversion at room temperature (a *retro*-Diels–Alder reaction) in *supra*, *supra* fashion.



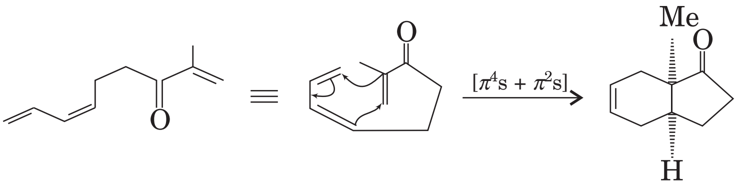
(e) A photochemically allowed [π^4s + π^4s] cycloaddition reaction between benzene and 1,3-butadiene takes place to give an unstable adduct containing a *trans*-double bond in an eight-membered ring. The adduct spontaneously dimerises at room temperature in [π^2s + π^2a] fashion to give the product with the desired stereochemistry.



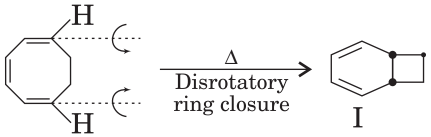
(f) Thermally allowed [π^2a + π^2s] cycloadditions of olefines are not observed because the antarafacial addition with respect to an olefin requires twisting about its original π bond is very difficult. However, ketenes undergo ready [2 + 2] cycloaddition reaction with alkenes in a [π^2s + π^2a] fashion in which the alkene always acts as the suprafacial component and ketene as the antarafacial component. This is due to the fact that a pair of interacting substituents are absent at one end of the reacting termini of the ketone (i.e., at the *sp*-hybridized carbon) and for this an orthogonal stable transition state is formed with the less hindered *sp* carbon of the ketene directed towards the more hindered side of the alkene double bond, i.e., C=O moiety of the ketene and the two Me groups of *cis*-2-butene remain on the same side. In fact, this addition occurs as a consequence of the fact that ketene has two sets of π orbitals at right angle to each other and overlap can be developed to orthogonal orbitals (dotted lines) and in addition there is transmission of information from one orbital to its orthogonal neighbour (bold line).



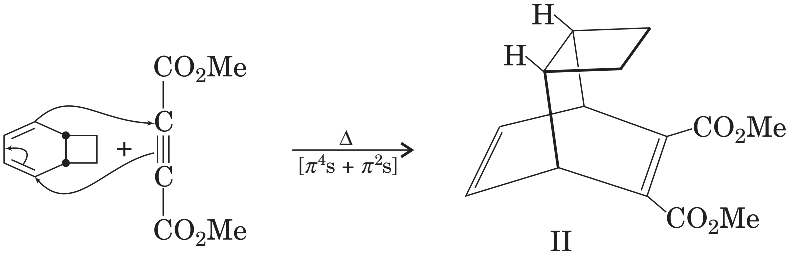
(g) This is a [π^4s + π^2s] thermally allowed intramolecular cycloaddition reaction (a Diels–Alder reaction) leading to the formation of a bicyclic *cis*-fused compound.



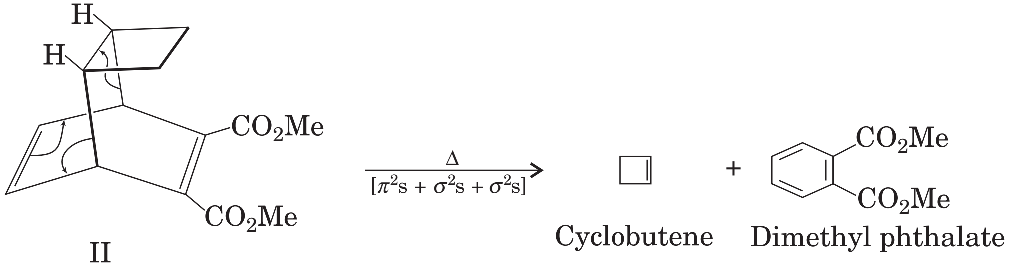
(h) This eight-membered triene (a 6π-electron system) undergoes thermally allowed disrotatory ring closure to form a *cis*-fused bicyclic compound (I).



In the next step, a $[\pi^4s + \pi^2s]$ thermally allowed cycloaddition reaction (a Diels–Alder reaction) occurs to give an adduct (II)

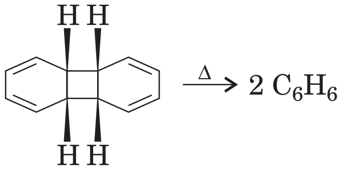


In the final step, the compound II undergoes a $[\pi^2s + \sigma^2s + \sigma^2s]$ cycloreversion (*retro*-Diels–Alder reaction) involving cleavage of bonds different from those from in the previous step.

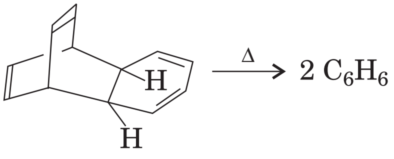


8. Which one of the following two thermal electrocyclic ring opening reaction is expected to take place and why? Show the FMO interactions involved in both the reactions.

(a)

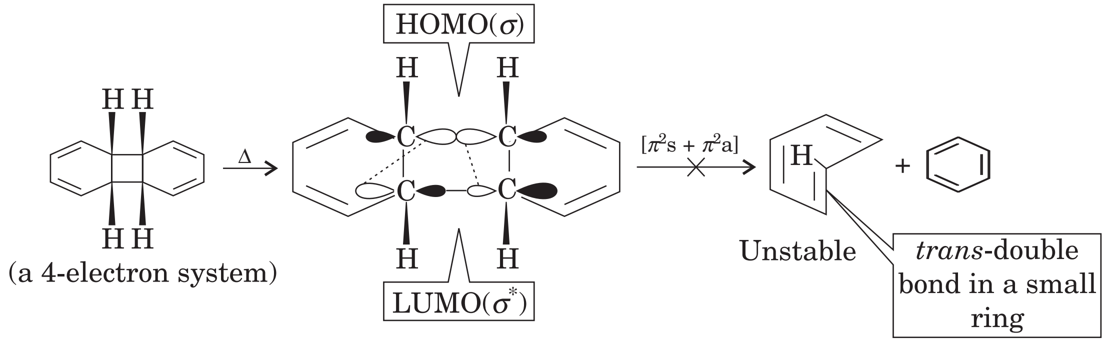


(b)

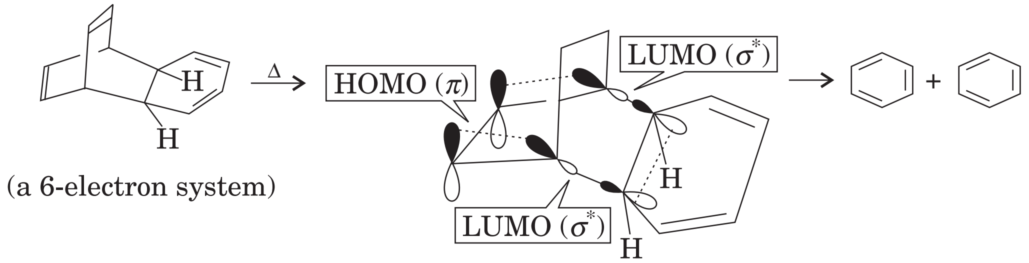


Solution

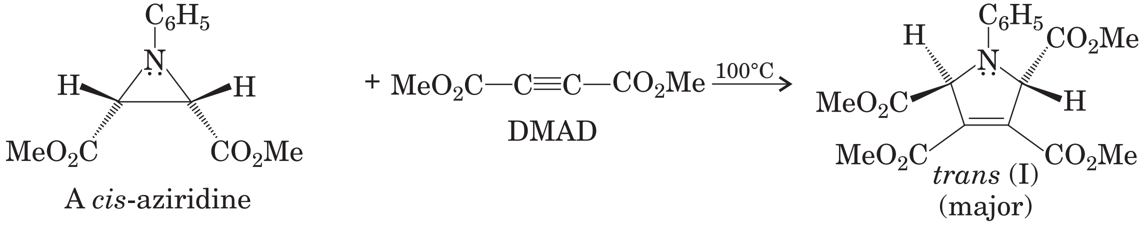
(a) This reaction does not take place because a [2 + 2] cycloreversion that must be a [σ^2s + σ^2a] process leads to the formation of a highly strained unstable cyclic triene with a *trans*-double bond in a small ring. Therefore, this reaction, although symmetry-allowed, does not take place.

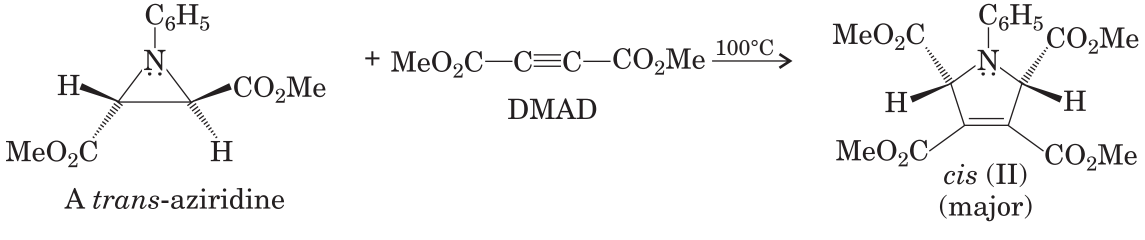


(b) This thermal symmetry-allowed [4 + 2] cycloreversion (a *retro*-Diels–Alder reaction) takes place through a [π^2s + σ^2s + σ^2s] process to give two benzene molecules.

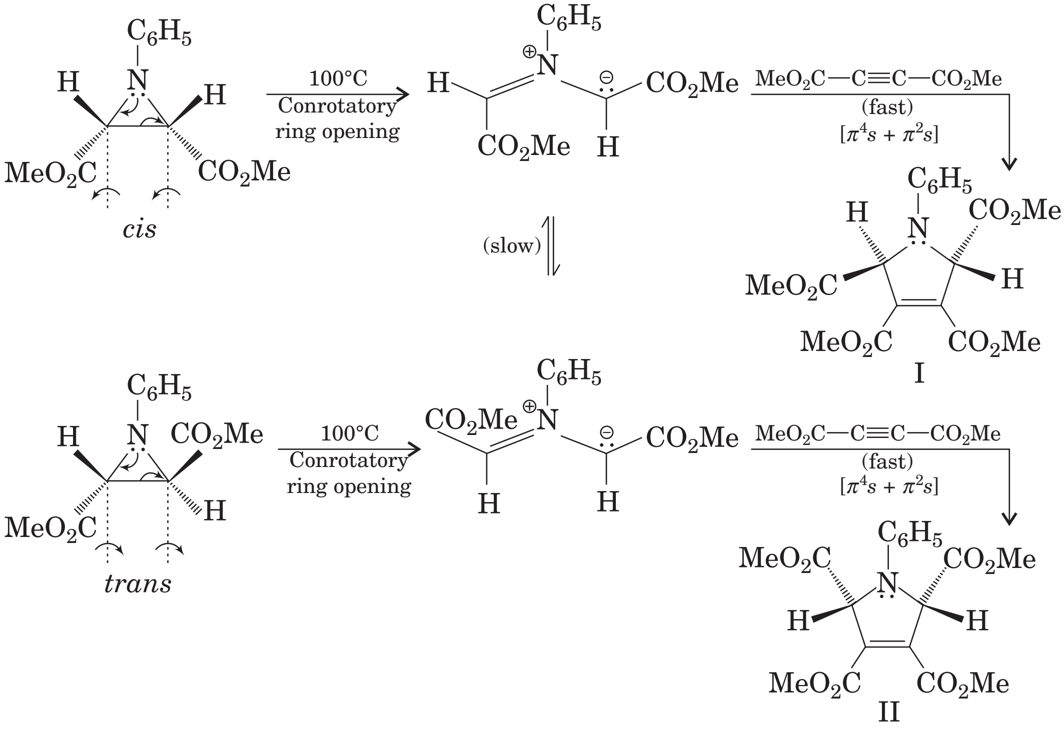


9. **When the following *cis*-aziridine is heated with DMAD, the compound I is obtained predominantly. However, when *trans*-aziridine is used, the isomeric compound II is obtained predominantly. Explain these observations and show the FMO interactions involved.**

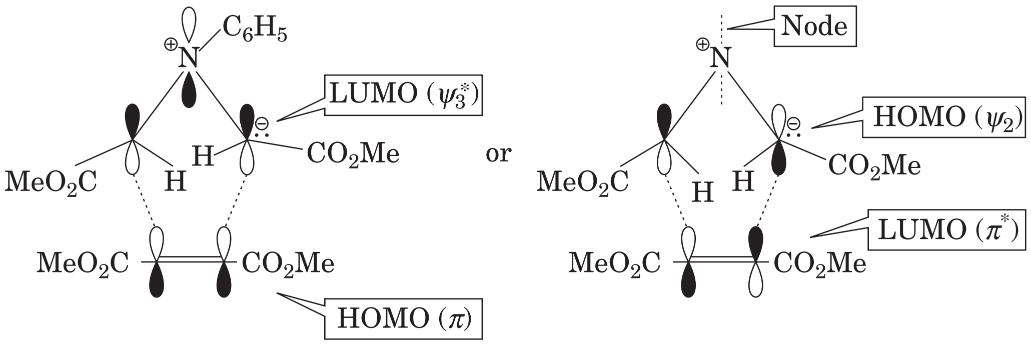




Solution Each of the two isomeric aziridine derivatives (a 4-electron system; two unshared pair of electrons on nitrogen and two electrons of the C—C σ bond) undergoes thermal ring opening in symmetry-allowed conrotatory fashion to give a 1,3-heterodipole which readily reacts with DMAD through a symmetry-allowed [π^4s + π^2s] process to give the product. Since the rate of interconversion of the two dipolar intermediates by C—N bond rotation is much slower compared to the rate of 1,3-dipolar addition, each of the reaction is stereoselective. The *cis*-aziridine produces the dihydro pyrrole I predominantly and the *trans*-aziridine produces the dihydro pyrrole II predominantly.

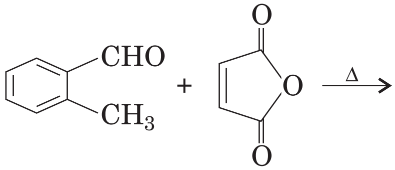


FMO interactions for this 1,3-dipolar cycloaddition reaction may be shown as follows:

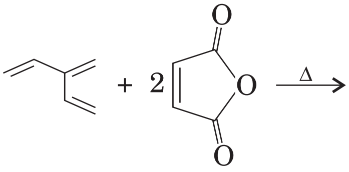


10. Write down the product expected to be formed in each of the following cycloaddition reactions:

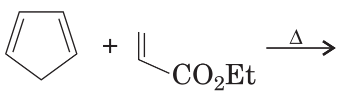
(a)



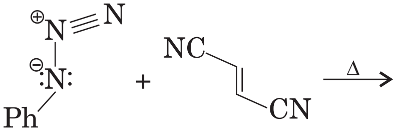
(b)



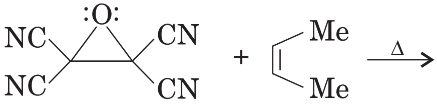
(c)



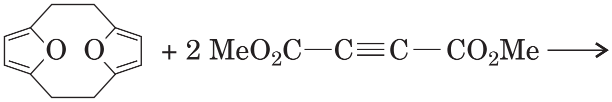
(d)



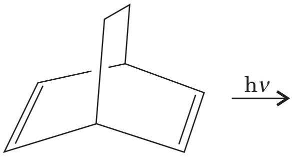
(e)



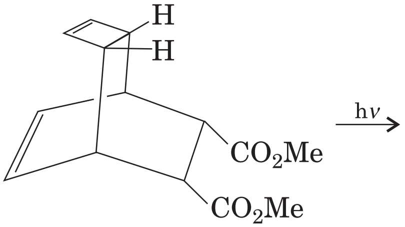
(f)



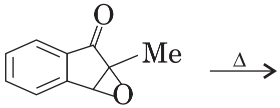
(g)



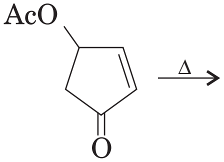
(h)



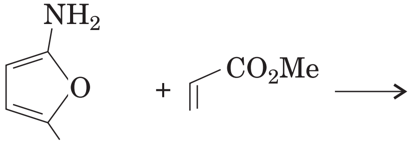
(i)



(j)

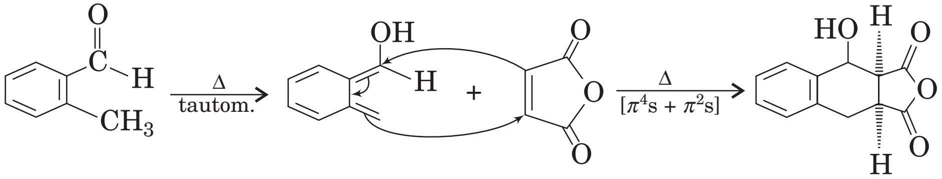


(k)

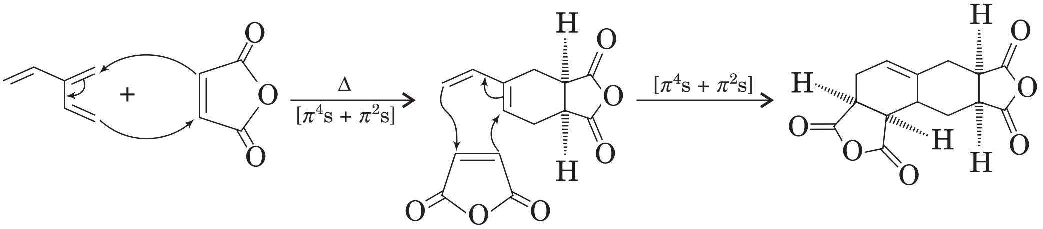


Solution

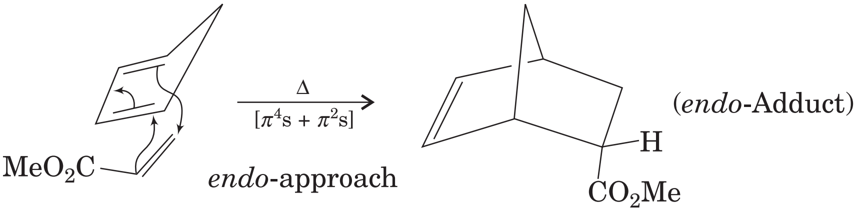
(a)



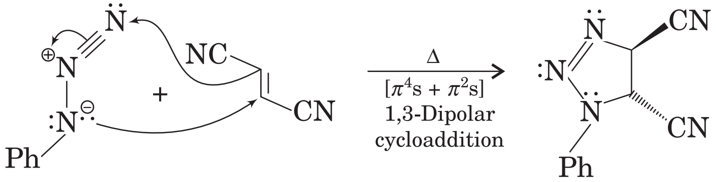
(b)


Δ
[π4s + π2s]
[π4s + π2s]
H
O
O
O

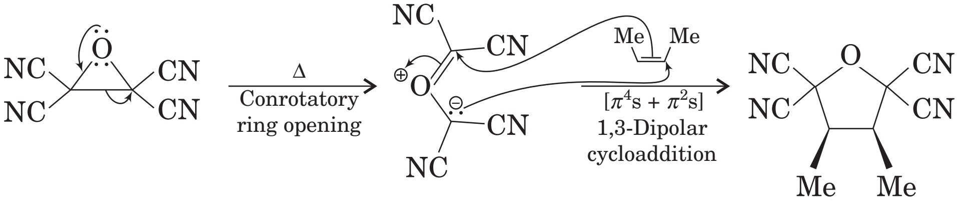
(c)


MeO2C
Δ
[π4s + π2s]
endo-approach
H
CO2Me
(endo-Adduct)

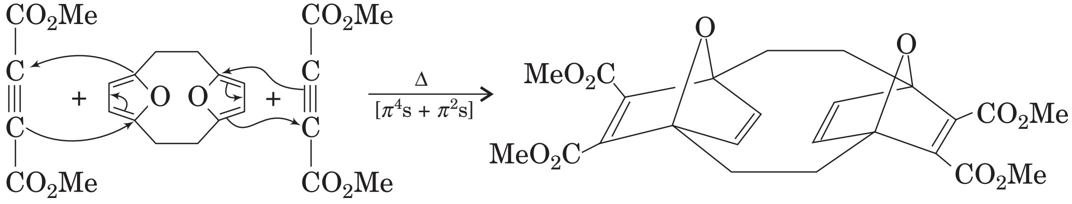
(d)


N
N
N
Ph
NC
CN
+
Δ
[π4s + π2s]
1,3-Dipolar
cycloaddition
Ph

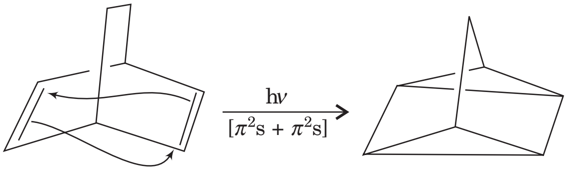
(e)


NC
NC
O
CN
CN
Δ
Conrotatory
ring opening
Me
Me
[π4s + π2s]
1,3-Dipolar
cycloaddition
Me
Me

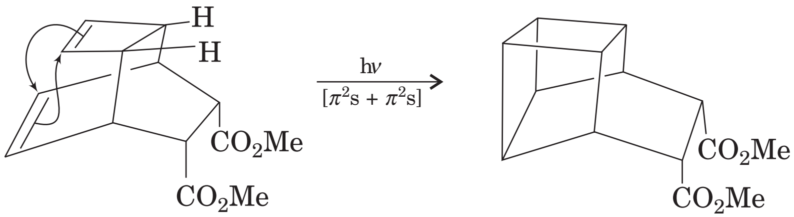
(f)

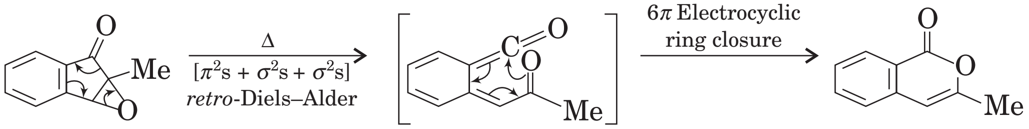

CO2Me
C
C
CO2Me
+
O
O
+
Δ
[π4s + π2s]
MeO2C
MeO2C
CO2Me
CO2Me

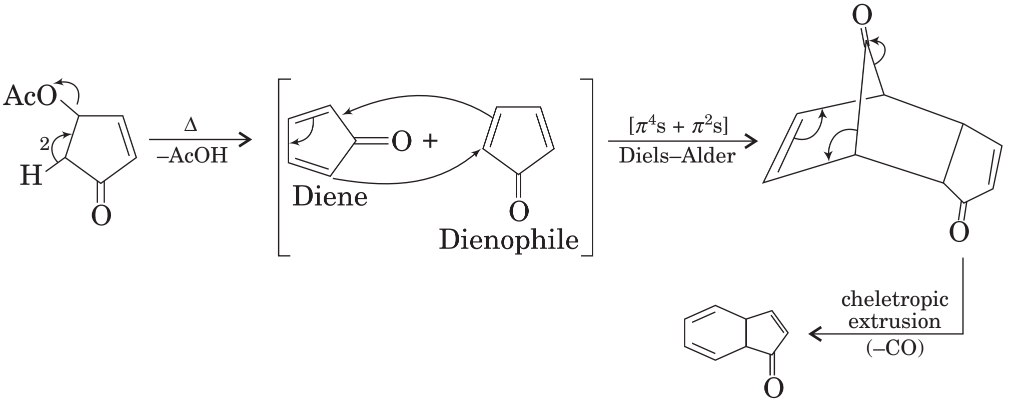
(g)

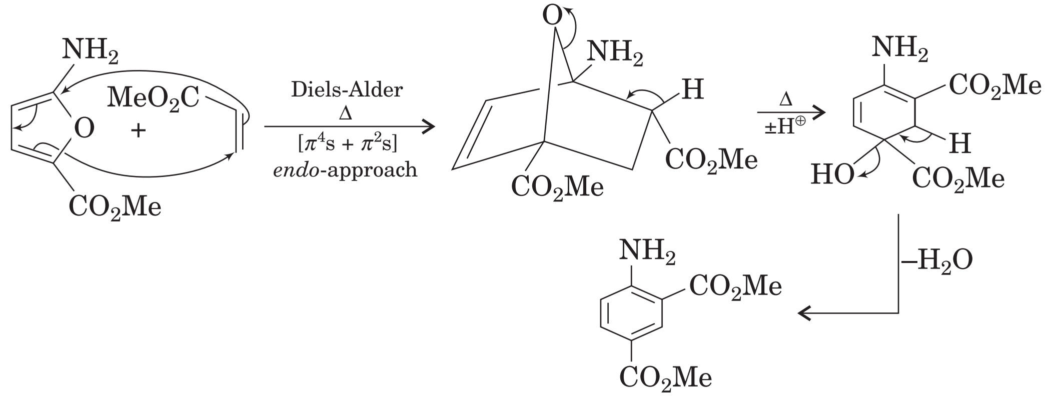

hν
[π2s + π2s]

(h)

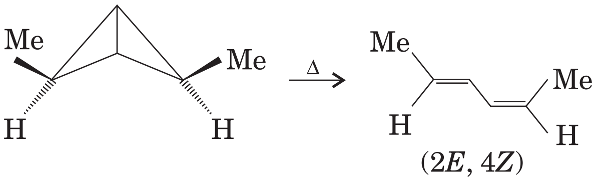

H
H
CO2Me
CO2Me
hν
[π2s + π2s]
CO2Me
CO2Me

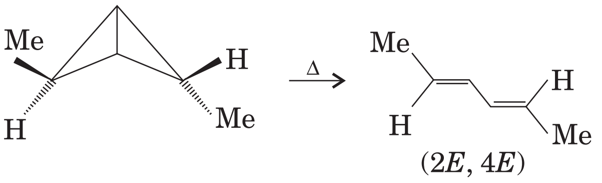
(i) 

(j) 

(k) 

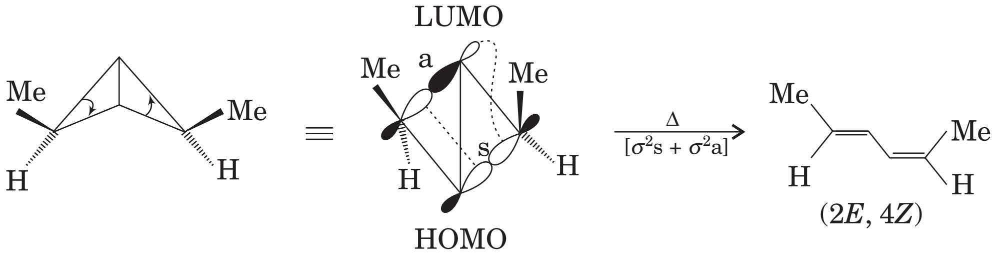
11. The following cycloreversions take place, when heat is applied. Assuming these are concerted reactions, show that they are [σ^2s + σ^2a] processes.

(a) 

(b) 

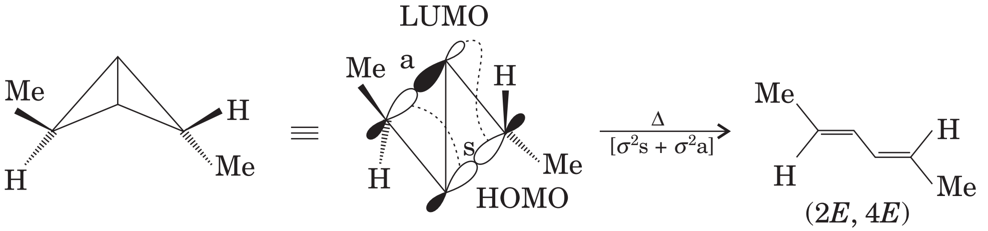
Solution

(a) The following diagram demonstrates that it is a [σ^2s + σ^2a] process which is thermally allowed.

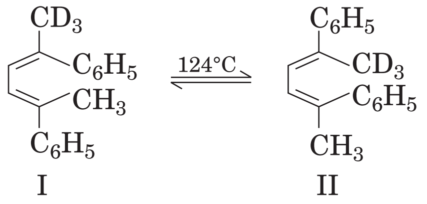


The stereochemistry of the product is also brought out by the above diagram. The σ bond (HOMO) opens up in conrotatory fashion and the other (LUMO) in disrotatory fashion.

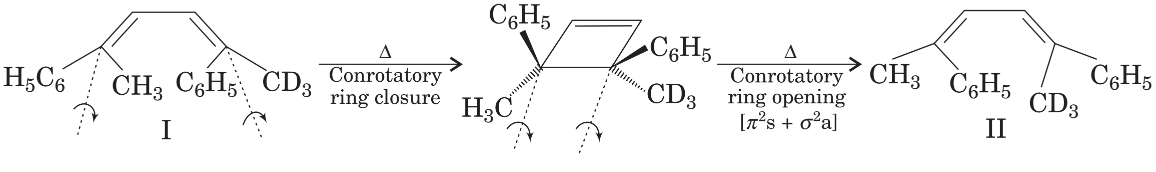
(b) The stereochemical outcome of this reaction becomes clear from the similar diagram as given below.



12. The butadienes, I and II, are easily interconverted under thermal condition, suggest a reasonable mechanism for this reaction.

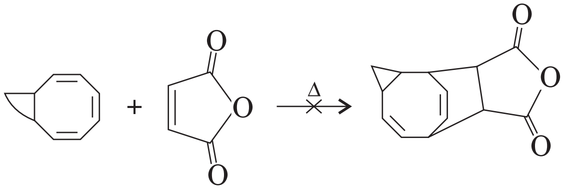


Solution The butadiene I undergoes thermally allowed conrotatory ring closure to give a *cis*-cyclobutane which then undergoes conrotatory ring opening to give the butadiene II.

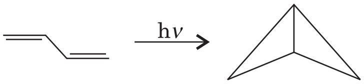


13. Explain the following observations:

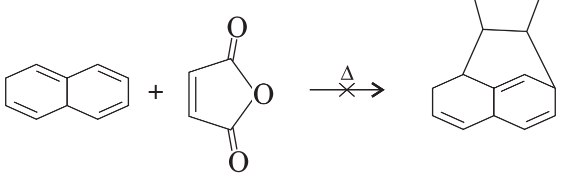
(a) The following [$\pi^4 s + \pi^2 s$] cycloaddition does not take place.



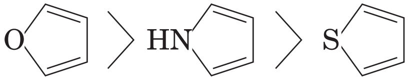
(b) Budadiene on irradiation gives, apart from cyclobutene, substantial amount of bicyclobutane.



(c)

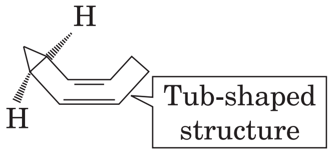


(d) The order of reactivity of pyrrole, furan and thiophene as diene in a Diels–Alder reaction is as follows:



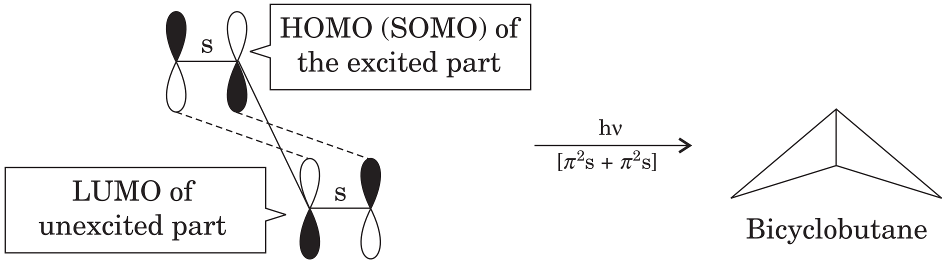
Solution

(a) The cyclopropane ring has characteristics of a double bond and the reactant bicyclic hydrocarbon has a tub-shaped structure as shown below.

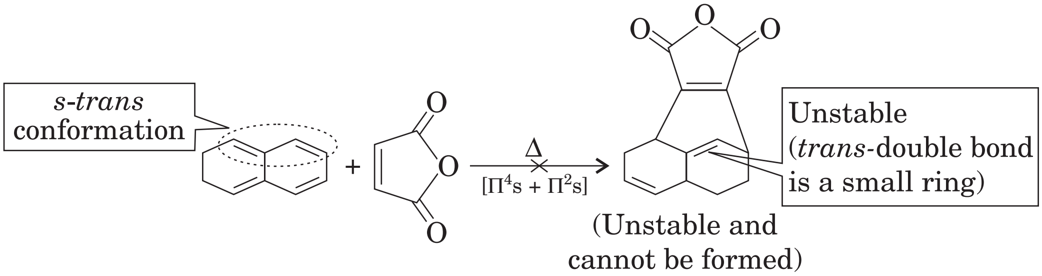


The double bonds in it are not conjugated enough to react with maleic anhydride which is not sufficiently reactive, i.e., [π^4s + π^2s] cycloaddition does not take place. More facile alternative reactions take place.

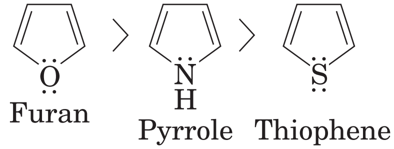
(b) The two ethylenic bonds may react as independent components. Since it is a photochemical cycloaddition, there is interaction between the HOMO of the excited part (SOMO) and LUMO of the unexcited part. It becomes clear from the diagram that the upper lobes of one overlap with the lower lobes of the other to give bicyclobutane by [π^2s + π^2s] process which is symmetry-allowed under photochemical condition.



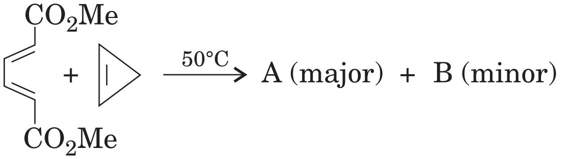
(c) When this tetraene is heated with maleic anhydride, the given adduct is not obtained because the conjugated diene component is to be involved in the reaction in *s-trans* conformation in which the terminal carbons are far apart from each other to form a six-membered transition state. Also, due to structural rigidity, it can never attain the *s-cis* conformation which is, in fact, mandatory for such a reaction to take place.


s-trans conformation
+
O
O
O
Δ
[Π⁴s + Π²s]
O
O
O
Unstable (trans-double bond is a small ring)
(Unstable and cannot be formed)

(d) The resonance energies of pyrrole, thiophene and furan are 88, 121 and 67 kJ mol^{-1}, respectively. Therefore, the order of aromaticity is: thiophene > pyrrole > furan. Hence, furan being least aromatic reacts readily with electron deficient dienophile. Pyrrole behaves as a diene only when an electron-attracting group is attached with nitrogen to make it less aromatic by withdrawing the unshared pair of electrons on nitrogen. Therefore, pyrrole is less reactive than furan as a diene. The most aromatic thiophene, under normal condition, does not behave as a diene but it can act as a diene under extreme conditions. So, the order reactivity of these three heterocycles is:

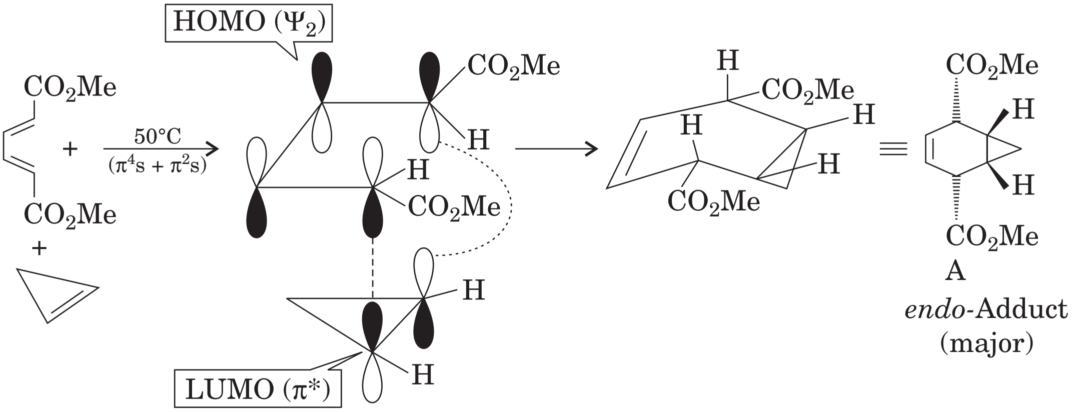


14. Predict the products of the following reaction by considering FMO interactions:



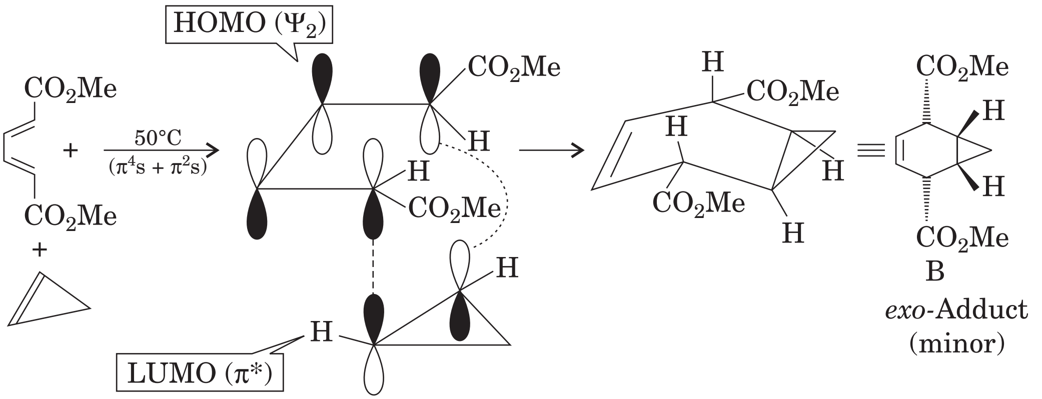
Solution Both the diene and the dienophile have substituents on the terminal carbons. Therefore, during the Diels–Alder reaction, they can add with each other in two orientations: *exo* and *endo*. Since the reaction is carried out at low temperature, the kinetically controlled *endo* product will be obtained as the major product (A). The transition state for the *exo* product is destabilized sterically and so, it will be formed as the minor product (B).

***endo*-Approach**



Transition state for *endo*-addition (more stable)

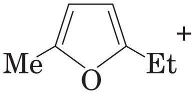
***exo*-Approach**



Transition state for *exo*-addition (less stable)

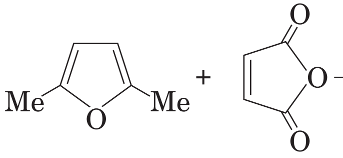
15. Identify the products A—M in the following reaction sequences:

(a)



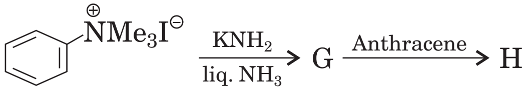
$+ \; MeO_2C—C\equiv C—CO_2Me \xrightarrow{\Delta} A \xrightarrow[\text{Pd}]{H_2\text{(1 mole)}} B \xrightarrow{\Delta} C + D$

(b)



$\longrightarrow E \xrightarrow{HBr} F$

(c)



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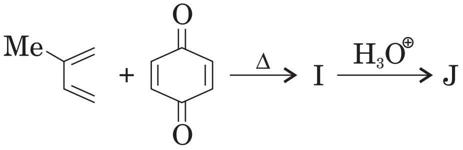

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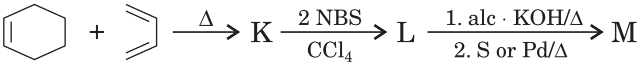

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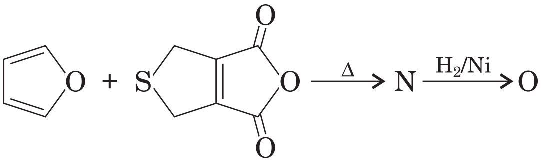
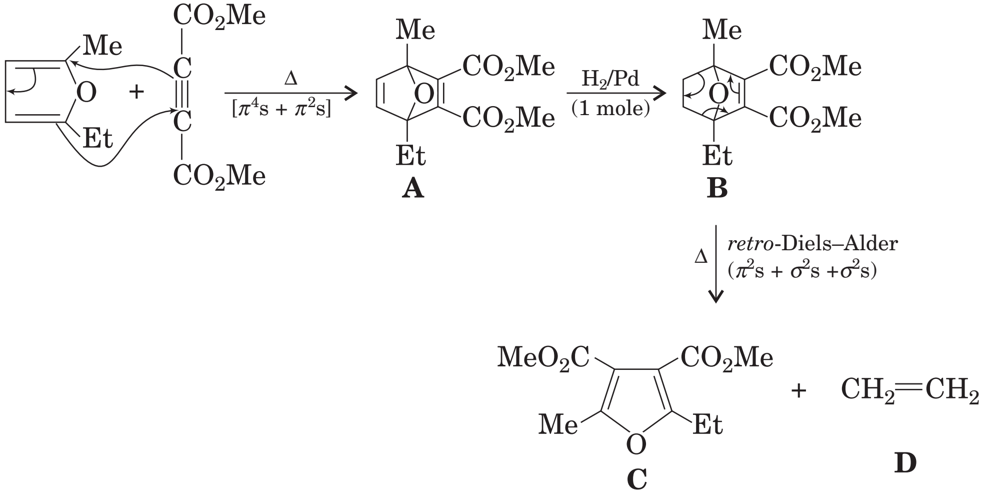


Solution

(a)



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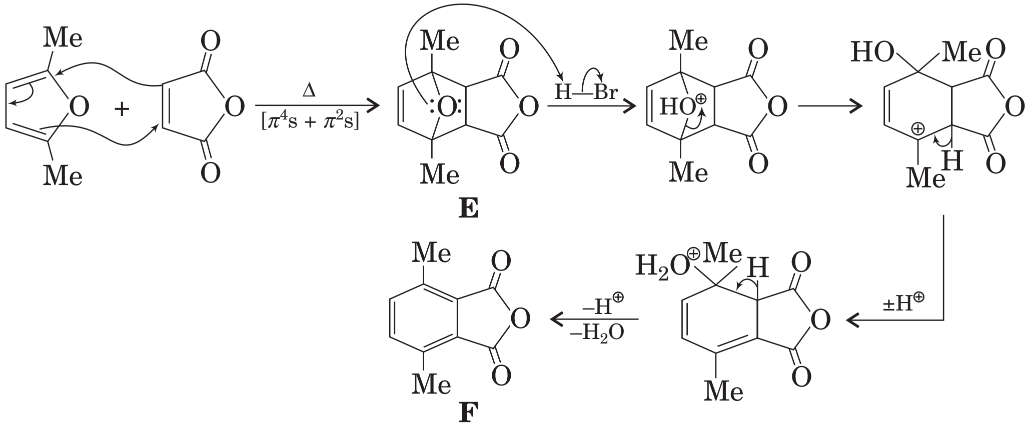

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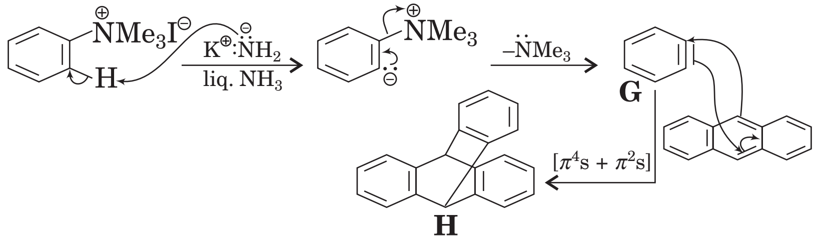
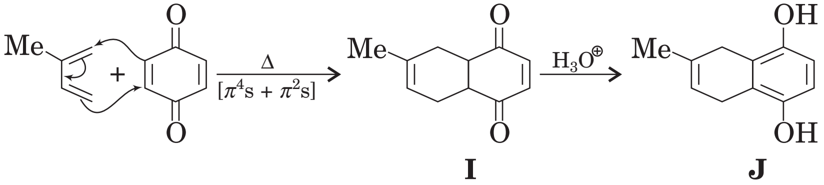
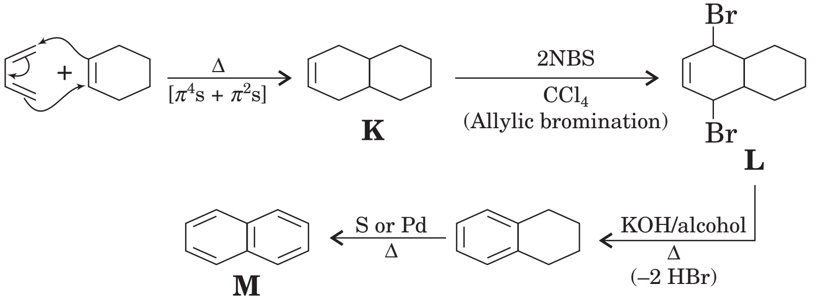


$\overset{\oplus}{N}Me_3I^{\ominus}$
H
$K^{\oplus}:\ddot{N}H_2^{\ominus}$
liq. NH_3
$\overset{\oplus}{N}Me_3$
$-\ddot{N}Me_3$
G
$[\pi^4s + \pi^2s]$
H

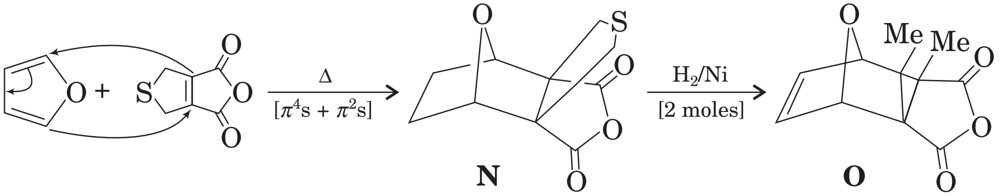
(d)



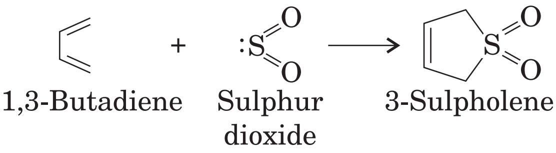
(e)



(f)

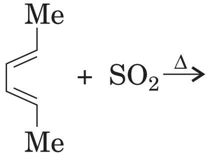


16. (a) Explain the following reaction on the basis of FMO considerations:

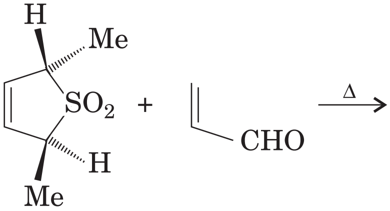


(b) Predict the product expected to be obtained in each of the following reactions:

(i)

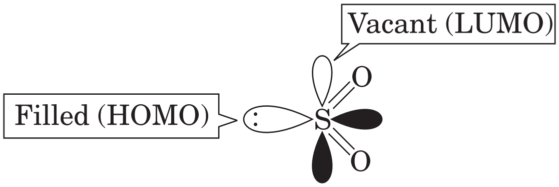


(ii)

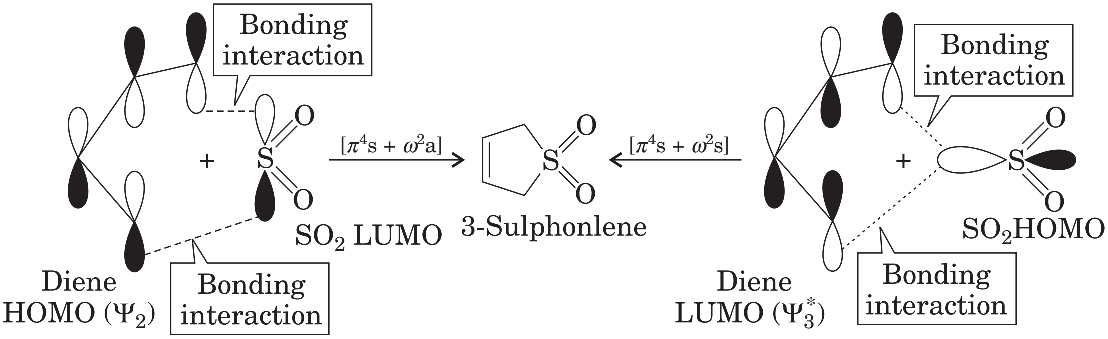


Solution

(a) Addition of SO_2 to 1,3-butadiene is an example of cheletropic reaction. The HOMO of SO_2 is that which has an unshaded pair of electrons in the plane of the atoms, while the LUMO represents the empty p-orbital perpendicular to this plane.

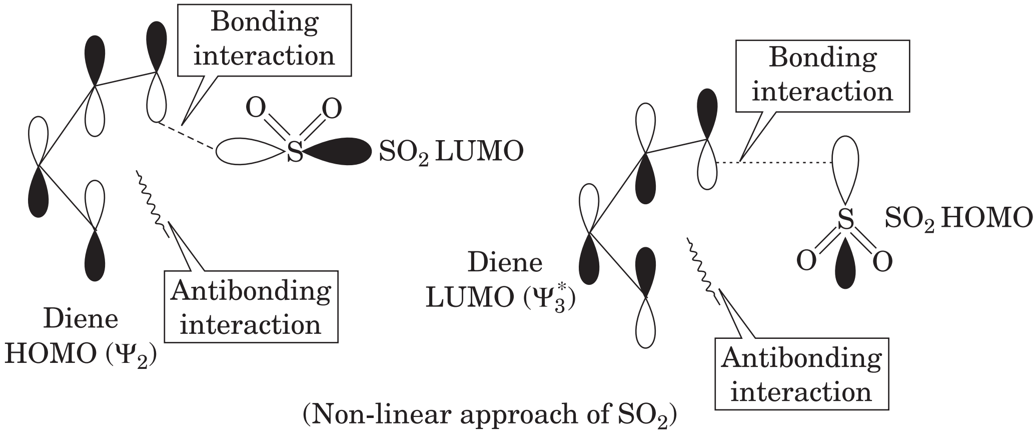


The terminal carbon atoms of the diene must move in the disrotatory manner in order to have a bonding interaction of the HOMO of the diene with the LUMO of SO_2 or the HOMO of SO_2 with the LUMO of the diene.



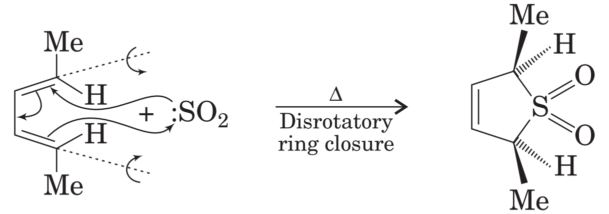
(Linear approach of SO_2)

It is clear from the above representation that the HOMO-LUMO interactions in the linear approach, oriented suprafacially to the 4π-electron system, are bonding. It is to be noted that the HOMO–LUMO interactions in the non-linear approach in which the 4π-electron system adds suprafacially are not bonding.



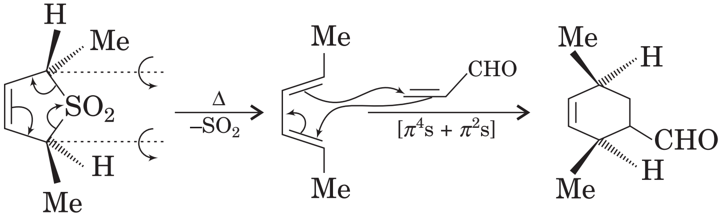
(Non-linear approach of SO_2)

(b) (i) The terminal p orbitals of the diene involved in this cheletropic reaction must move in disrotatory manner in order that HOMO–LUMO interactions can take place in a bonding way. Because of disrotatory mode of ring closure, the outer methyl group in the diene become *cis*- to each other in the product.



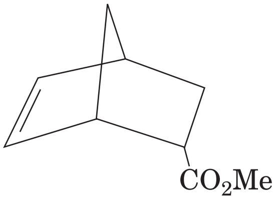
(2*E*, 4*E*)-2,4-Hexadiene A *cis*-sulpholene

(ii) When heated at a high temperature, 3-supholene generates 2,4-hexadiene in a reverse cheletropic reaction. A [π^4s + π^2s] cycloaddition (a Diels–Alder reaction) then takes place between butadiene and the olefin to form the *cis*-adduct.



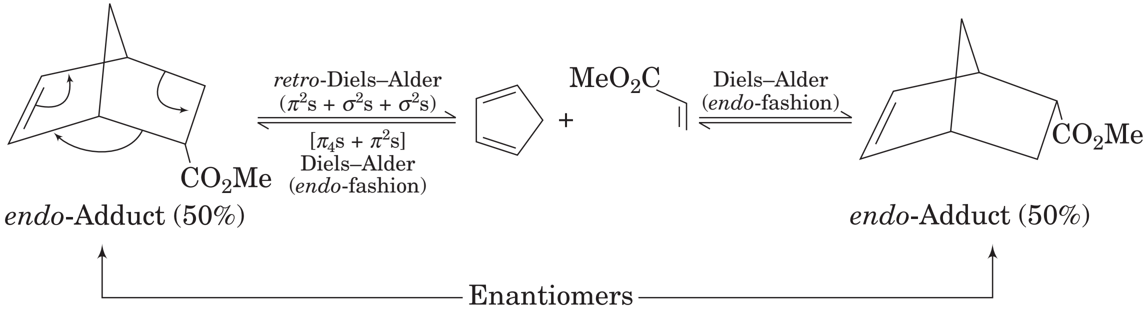
cis-Adduct

17. When the following optically active ester is heated at 100°C, it undergoes racemization. Explain this observation.

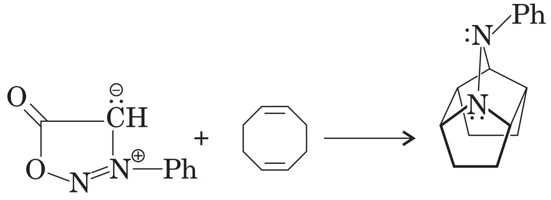


Solution Since the Diels–Alder reaction is reversible in nature, this optically active bicyclic compound undergoes *retro*-Diels–Alder reaction on heating at 100°C to give cyclopentadiene and methyl acrylate reversibly. These two components combine again to give the starting compound or combine in another *endo* fashion to give its enantiomer.

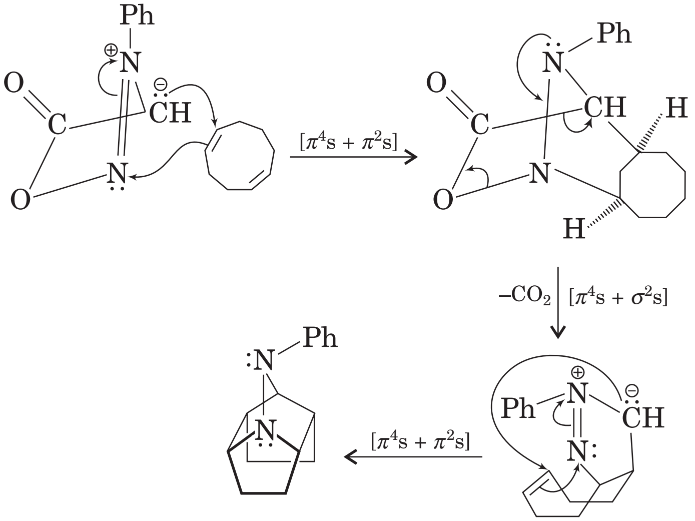
So, the starting optically active bicyclic compound is found to racemize on heating at 100°C.



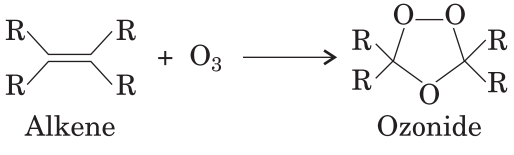
18. The following transformation is an example of 1,3-dipolar cycloaddtion. Explain with a suitable diagram.



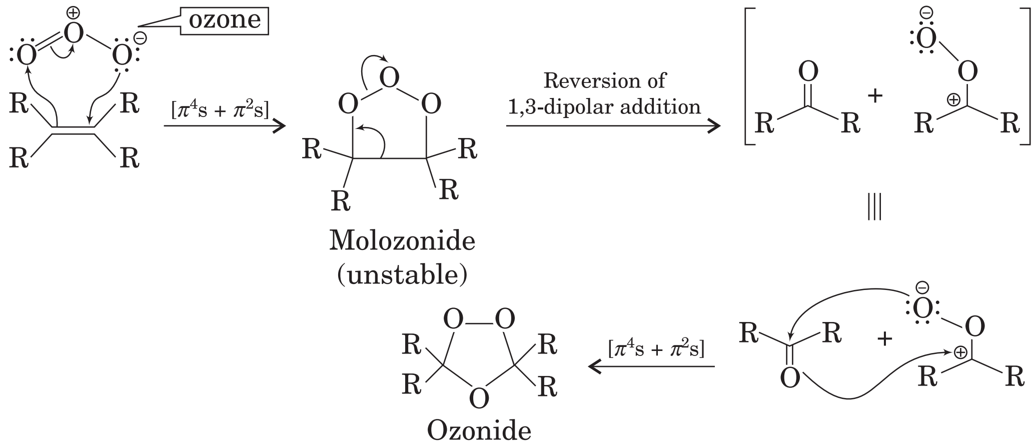
Solution This transformation involves a 1,3-dipolar cycloaddition followed by decarboxylation and another 1,3-dipolar addition (intramolecular).



19. Provide FMO rationalization for the formation of ozonide from ozone and an alkene:



Solution The addition of ozone to an alkene is an example of a 1,3-dipolar cycloaddition reaction. Thus, the ozonide formation reaction can be analyzed in terms of a series of three concerted reactions. Ozone is a 4π-electron system. Therefore, formation of the unstable molozonide occurs through the [π^4s + π^2s] process. Reversion of 1,3-dipolar addition occurs when molozonide dissociates to give a carbonyl compound and a zwitterion. These two then combine through a [π^4s + π^2s] process to give the ozonide.



STUDY PROBLEMS

1. Predict the product expected to be formed in each of the following reactions:

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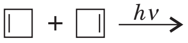
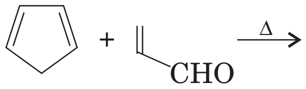
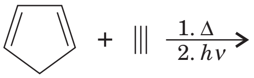


(b)


(c)


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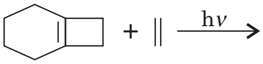
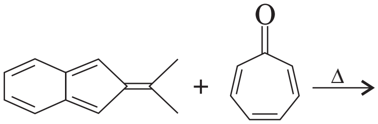
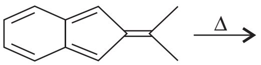
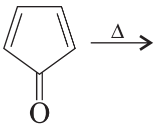
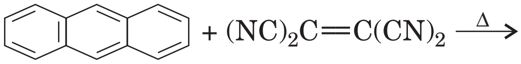


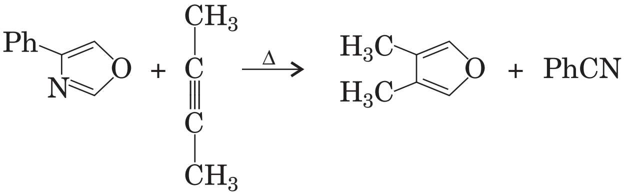
(e)


(f) 2


(g) 2


(h)


2. Suggest a mechanism for each of the following reactions:

(a)


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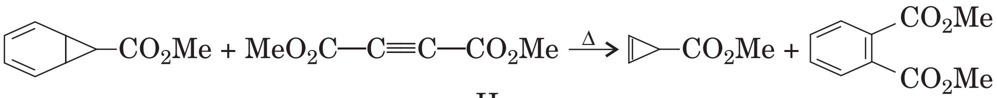

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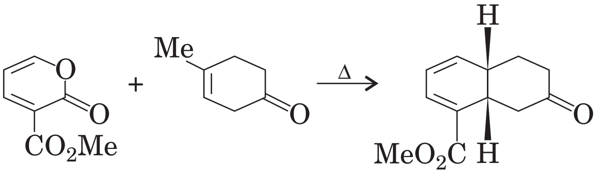
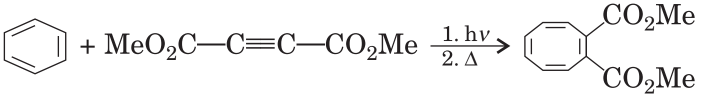
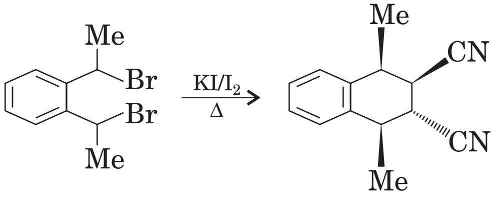
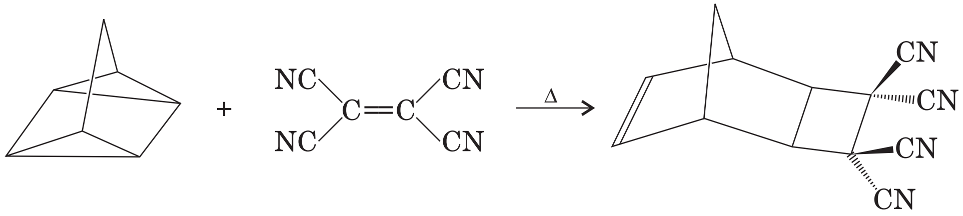
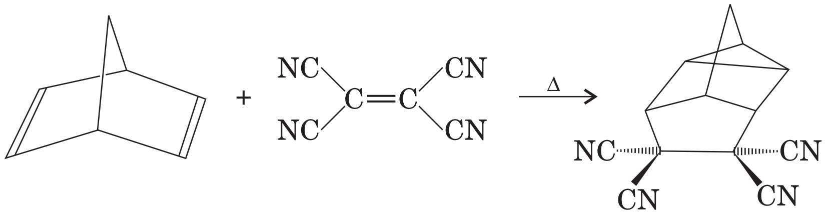
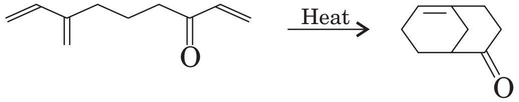


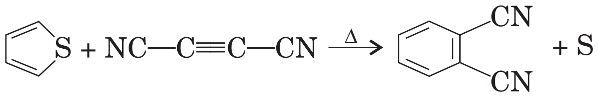
(d) 

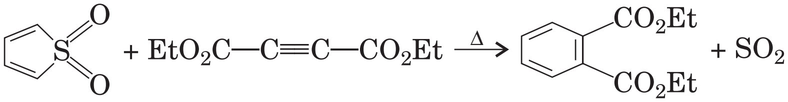
(e) 

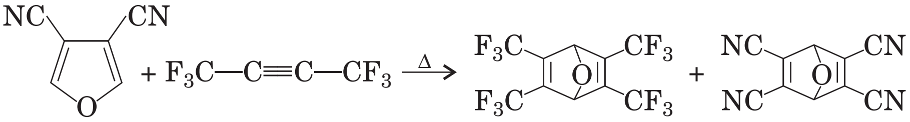
(f) 

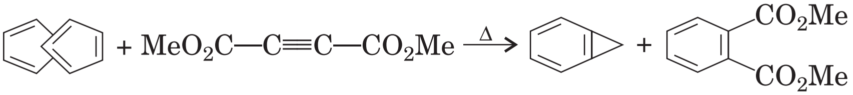
(g) 

(h) 

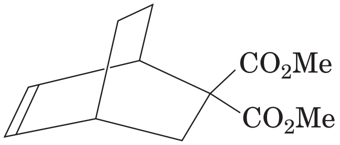
(i) 

(j) 

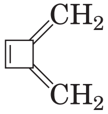
(k) 

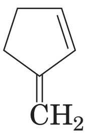
(l) 

3. Write down the possible combinations of the diene and dienophile that would react in a Diels–Alder reaction to give the following bicyclic compound. Predict the better combination.



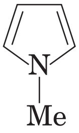
4. Explain why the following dienes or diyne do not react with tetracyanoethylene to give an adduct:

(a) 

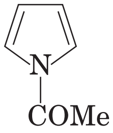
(b) 

(c) HC≡C—C≡CH

5. The compound A does not undergo the Diels–Alder reaction with DMAD but the compound B does. Explain.

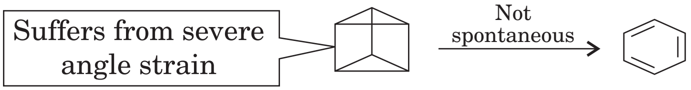


A



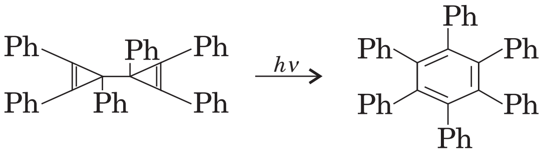
B

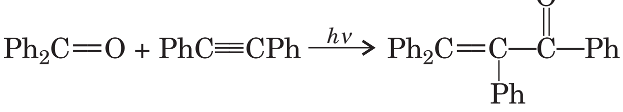
6. Despite the tremendous amount of strain in prismane, its transformation to benzene (a stable aromatic system) is not spontaneous. Explain.



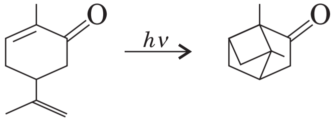
Prismane Benzene

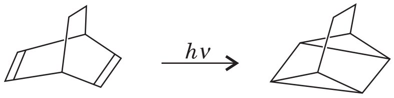
7. Provide an FMO rationalisation for each of the following photochemical transformations:

(a) 

(b) 

$$Ph_2C{=}O + PhC{\equiv}CPh \xrightarrow{h\nu} Ph_2C{=}\underset{\displaystyle Ph}{C}{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}Ph$$

(c) 

(d) 

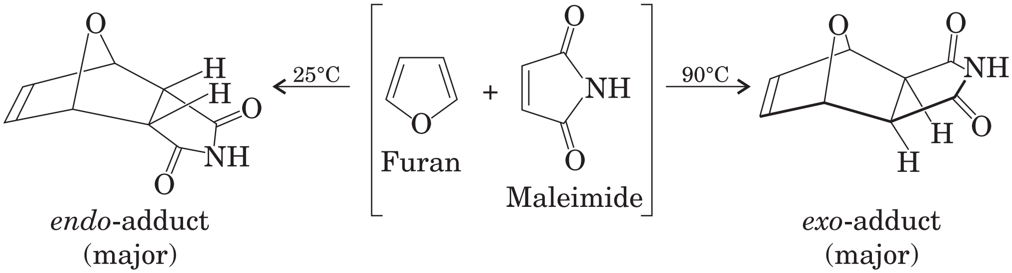
8. Predict the product(s) obtained in each of the following reactions:

(a) *cis*- $PhCH{=}CHPh + Ph{-}\overset{\oplus}{C}{=}N{-}\overset{\ominus}{\ddot{N}}Ph \xrightarrow{\Delta}$

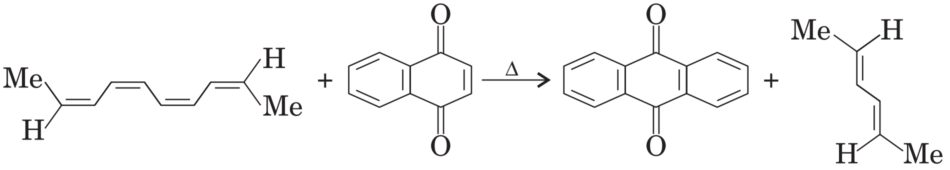
(b) *trans*- $PhCH{=}CHPh + Ph{-}\overset{\oplus}{C}{=}N{-}\overset{\ominus}{\ddot{N}}Ph \xrightarrow{\Delta}$

Give stereochemistry of the product in both the dipolar additions.

9. Furan and maleimide undergo a Diels–Alder reaction at 25°C to give the *endo*-adduct as the major product. However, when the reaction is carried out at 90°C, the major product is the *exo*-adduct. Explain and rationalize on the basis of FMO interactions.

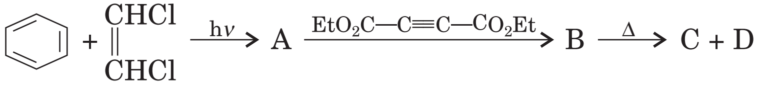


10. Explain the following transformation in terms of four successive pericyclic reactions of which the first one does not involve the quinone moiety.

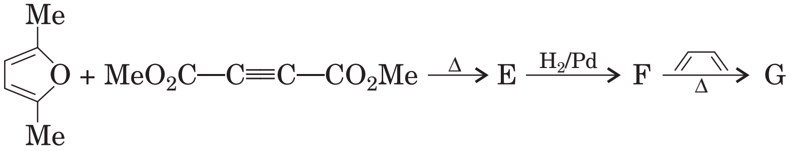


11. Provide structures for the compounds A—R in the following reaction sequences:

(a)



(b)



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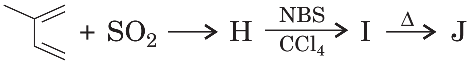
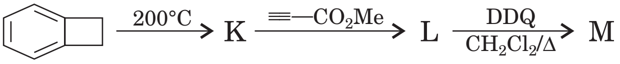
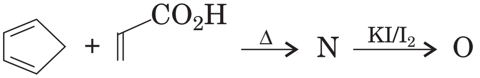


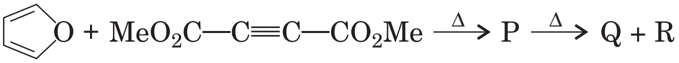
(d)



(e)

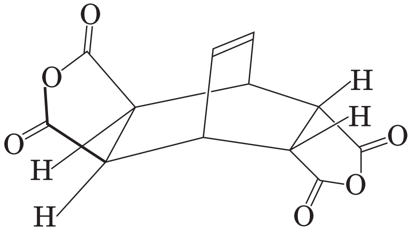


(f)

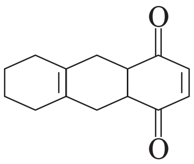


12. Outline the synthesis of each of the following compounds using the Diels–Alder reaction in one or more of the steps involved:

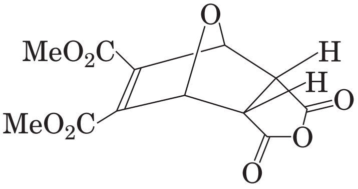
(a)



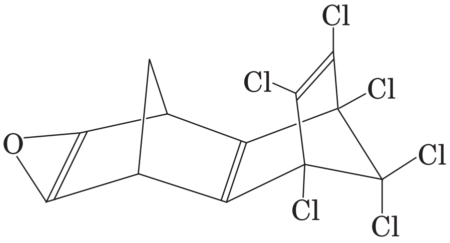
(b)



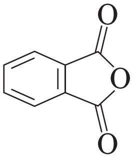
(c)



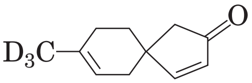
(d)



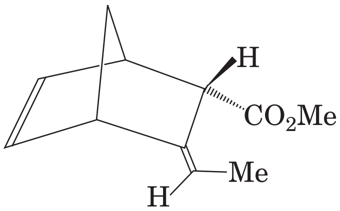
(e)



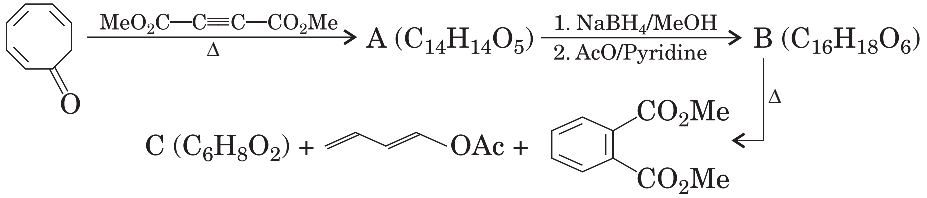
(f)



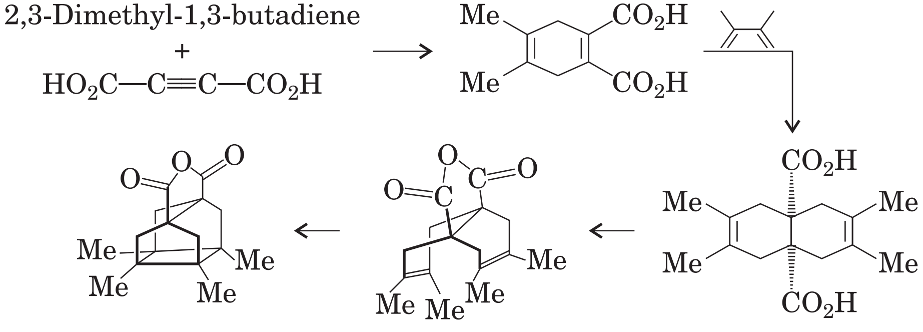
13. Write down the structure of the chiral allene which forms the following Diels–Alder adduct with cyclopentadiene.



14. Suggest a mechanism for each thermolysis step and assign structures to A, B and C in the following reaction sequence:

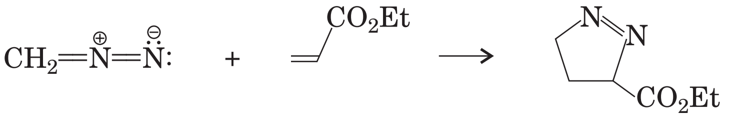


15. Classify each of the following steps and determine the reaction condition for it:



[**Hint:** The first step is a thermally allowed [π^4s + π^2s] process. The second step is also a [π^4s + π^2s] process and thermally allowed. The third step is a facile thermal dehydration as the two –COOH groups are *cis* and close to each other and the fourth step is an intramolecular [$\pi^2s + \pi^2s$] cycloaddition which is photochemically allowed forming an all-*cis*-substituted cyclobutane ring.]

16. Explain the following 1,3-dipolar cycloaddition reaction by FMO approach:



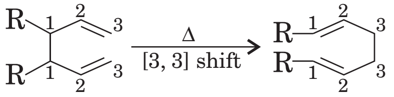
Diazomethane Ethyl acrylate A dihydropyrazole

8.4 SIGMATROPIC REACTIONS (REARRANGEMENTS)

Introduction

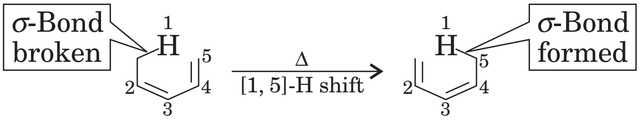
There are another class pericyclic reactions in which a σ-bonded atom or group migrates from one end of a π-system to the other (equivalent to the migration of a σ-bond) or a σ-bond flanked by 2π-electron systems migrates to a new position within the molecule in an uncatalyzed intramolecular process. These reactions are known as sigmatropic rearrangements.

When both the termini of a σ-bond move, say one from C-1 to C-*i* and another from C-1 to C-*j*, it is referred to as [*i*, *j*] order of sigmatropic rearrangement. For example, in the following reaction (known as *Cope rearrangement*), a σ-bond migrates from C-1 to C-3 position. Therefore, it is a sigmatropic shift of the order [3,3], since *i* and *j* both correspond to 3.



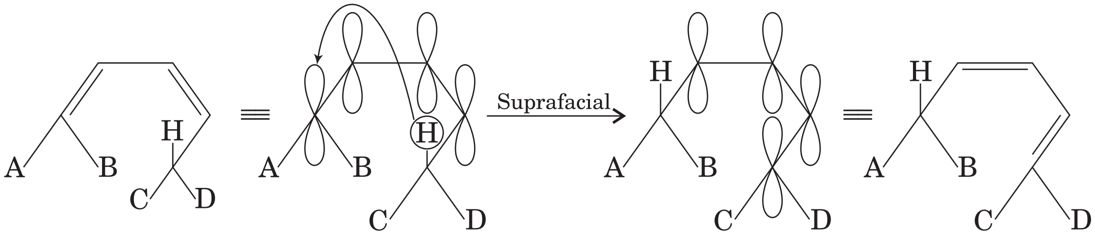
A [3, 3] sigmatropic rearrangement

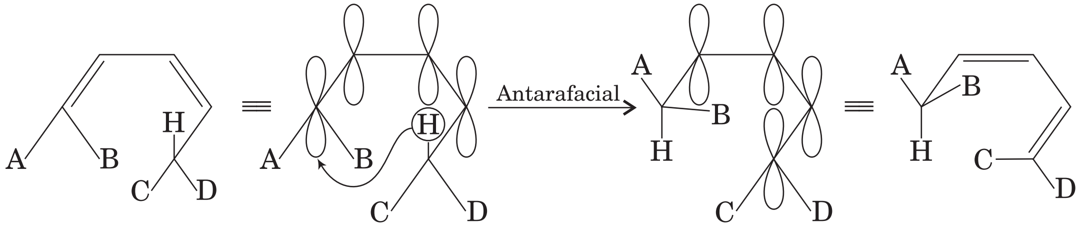
When one end of a σ-bond moves from C-1 to a carbon numbered *j*, but the other end remains attached to the migrating atom, it is referred to as [1, *j*] order of sigmatropic rearrangement. For example, the following sigmatropic rearrangement is of the order [1,5] because hydrogen migrates from C-1 to C-5 ($j = 5$); the other end of the σ-bond is still attached to hydrogen ($i = 1$).



A [1, 5] sigmatropic rearrangement

Stereochemical course Since a sigmatropic reaction involves migration of a σ-bond across the π-electron system, there are two possible stereochemical courses by which the process may take place. When the migrating σ-bond moves across the same face of the π-system, it is called a *suprafacial* process and when it moves across the opposite face of the π-system, it is called an *antarafacial* process. The following [1,5] sigmatropic shift of hydrogen illustrates the two possible courses:



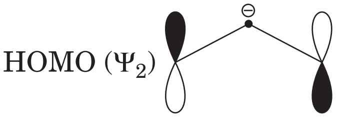


Suprafacial migration is more common than the antarafacial migration as the latter process consists of a more strained cyclic transition state. However, the antarafacial migration may take place for long range migrations like [1,7] H shift and this is because a large ring in transition state may tolerate the imposed strain.

8.4.1 FMO Rationalization for the Sigmatropic Shift of Hydrogen

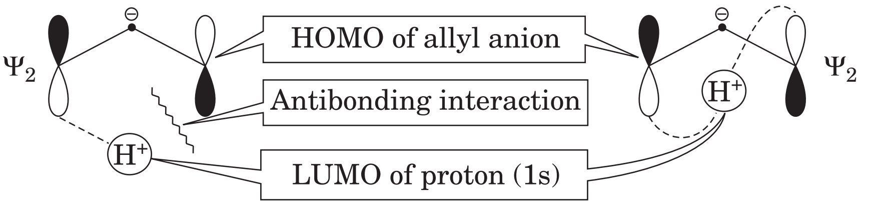
8.4.1.1 [1,3] Shift of Hydrogen

Thermal reaction In FMO analysis, the [1,3] sigmatropic shift of hydrogen may be treated as the interaction of the proton LUMO (an empty 1s orbital) with the HOMO of allyl anion which is shown below:



Allyl anion

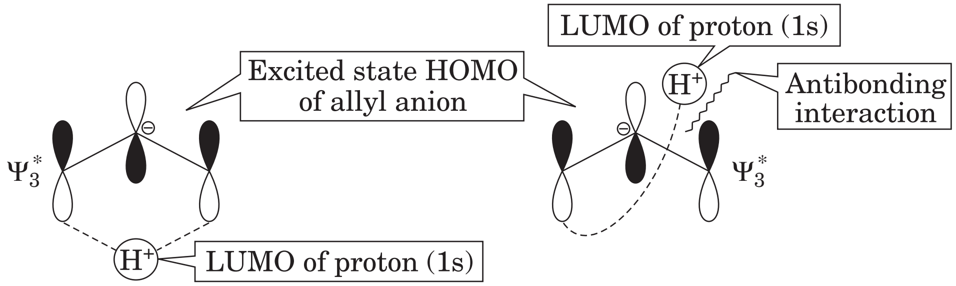
The hydrogen atom must move to a lobe of same phase sign. The suprafacial shift of hydrogen is not allowed because this leads to an antibonding (out-of-phase) interaction. For in-phase bonding interaction the shift must be antarafacial. Although the antarafacial shift of hydrogen is symmetry-allowed, it does not take place because it is sterically very difficult. In fact, for bridging opposite lobes by the migrating hydrogen the π system is to be twisted far from planarity that requires for effective electron delocalization. Such a cyclic transition state is highly strained (unstable) and very difficult to achieve in a concerted reaction. Therefore, the thermal [1,3]-shift of hydrogen is not at all observed.



Thermal [1, 3] suprafacial shift of H: *symmetry-forbidden*

Thermal [1, 3] antarafacial shift of H: *symmetry-allowed* but geometrically not feasible

Photochemical reaction In photo-induced reaction, i.e., in the excited state of an electron from ψ_2 of allyl anion to ψ_3^* takes place and therefore, ψ_3^* is now the HOMO of the allyl anion. Suprafacial [1,3] shift of hydrogen is now symmetry-allowed, but the antarafacial shift is symmetry-forbidden (i.e., leads to an antibonding interaction). Again, the suprafacial migration imposes no steric strain in the transition state of this concerted reaction. Hence, photochemical [1,3] shift of hydrogen is facile and takes place readily.

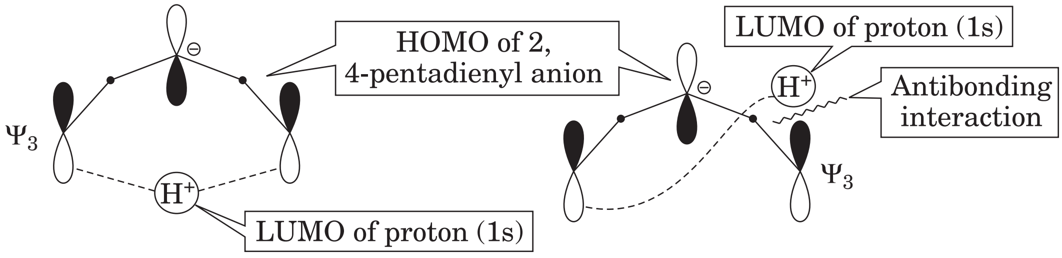


Photochemical [1,3] suprafacial shift of H: *symmetry-allowed*

Photochemical [1,3] antarafacial shift of H: *symmetry-forbidden*

8.4.1.2 [1,5] Shift of Hydrogen

Thermal reaction [1,5] shift of hydrogen may be considered as the interaction of the proton LUMO (an empty 1s orbital) with the HOMO of 2,4-pentadienyl anion. Thermal [1,5] suprafacial shift of hydrogen is symmetry-allowed because in this reaction hydrogen moves to a lobe of same phase sign. However, the antarafacial migration is symmetry-forbidden as it leads to an unfavourable antibonding interaction.

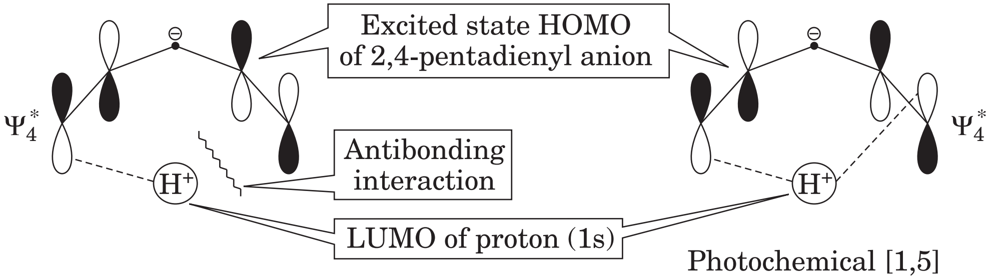


Thermal [1,5] suprafacial shift of H: *symmetry-allowed*

Thermal [1,5] antarafacial shift of H: *symmetry-forbidden*

Since the suprafacial migration of hydrogen does not involve any distortion or strain in the transition state, thermal [1,5] shift of hydrogen is facile and very common.

Photochemical reaction In photo-induced reaction, i.e., in the excited state, it is ψ_4^* which is the HOMO of the pentadienyl radical and in this case, antarafacial shift of hydrogen is symmetry allowed but suprafacial shift of hydrogen is symmetry forbidden. However, the antarafacial shift is extremely difficult from geometric point of view, even though it is symmetry-allowed.



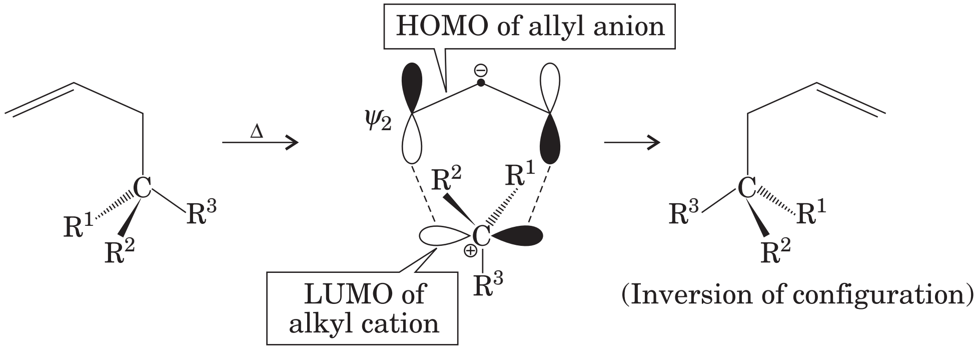
Photochemical [1,5] suprafacial shift of H: *symmetry-forbidden*

Photochemical [1,5] antarafacial shift of H: *symmetry-allowed* but geometrically difficult

8.4.2 FMO Rationalization for the Sigmatropic Shift of Carbon

8.4.2.1 [1,3] Shift of Carbon

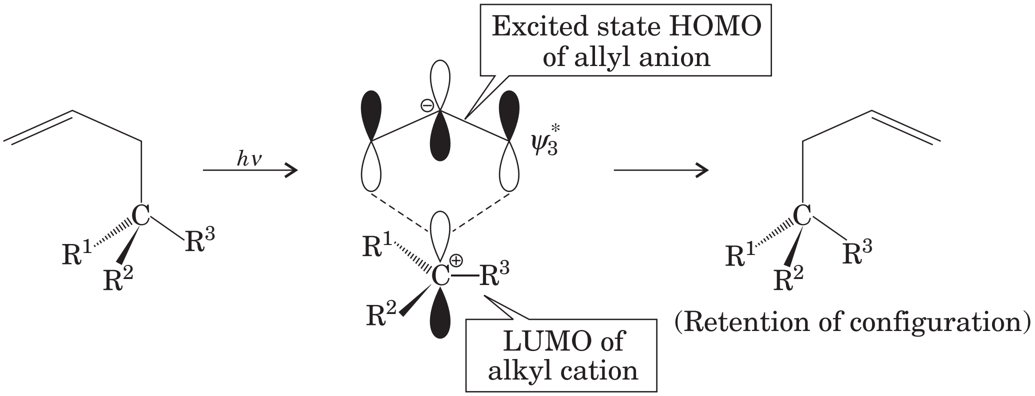
Thermal reaction In FMO analysis, the [1,3] shift of carbon is treated as a case in which an alkyl cation migrates from one end to the other of an allyl anion and LUMO of the alkyl cation (an empty *p* orbital) interacts with the HOMO (ψ_2) of an alkyl anion. For bonding overlap to take place, the alkyl cation acts as the antarafacial component and the π-system acts as the suprafacial component. Therefore, the migration which occurs with inversion of configuration at the migrating alkyl group is symmetry-allowed.



Thermally allowed [1,3] shift of carbon:
supra-antara with inversion of configuration

The *supra-supra* migration of the alkyl cation is a symmetry-forbidden process and the antarafacial migration with respect to the allylic system, i.e., the *antara-supra* shift of alkyl cation is, although symmetry-allowed, geometrically not feasible.

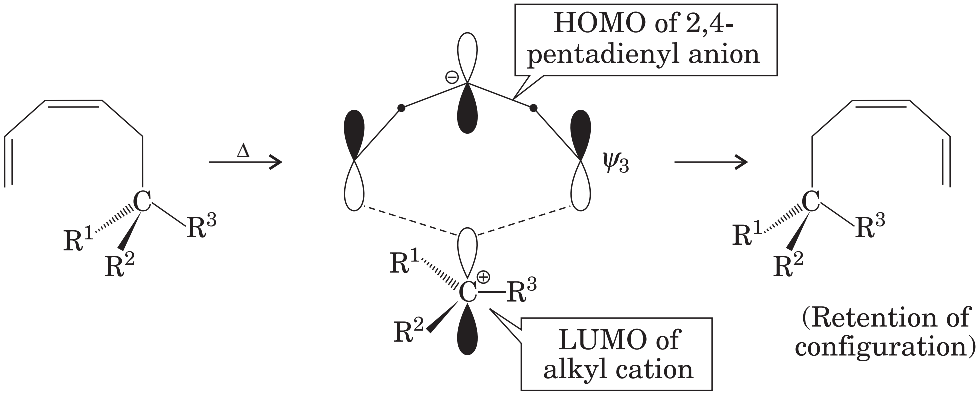
Photochemical reaction In photo-induced [1,3] shift of carbon, it is ψ_3^* (the excited state HOMO) of allyl anion which interacts with the LUMO of alkyl cation. Thus, the bonding overlap *supra-supra* shift of carbon occurs and there is retention of configuration at the migrating group.


Excited state HOMO of allyl anion
$h\nu$
ψ_3^*
R^1
R^2
R^3
C
LUMO of alkyl cation
(Retention of configuration)

Photochemically allowed [1, 3] shift of carbon:
supra-supra with retention of configuration

8.4.2.2 [1,5] Shift of Carbon

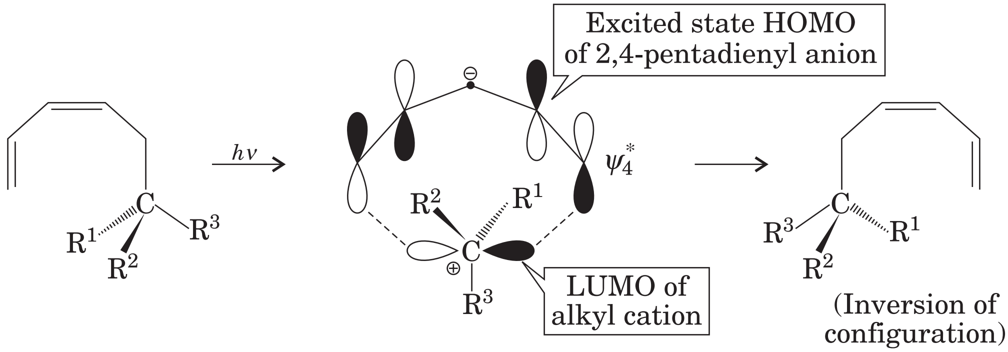
Thermal reaction In FMO analysis the [1,5] shift of carbon is treated as a case in which an alkyl cation migrates from one end to the other of 2,4-pentadienyl anion and LUMO of the alkyl cation (an empty *p* orbital) interacts with the HOMO (ψ_3) of 2,4-pentadienyl anion. The alkyl cation as well as the π-system acts as suprafacial component for undergoing bonding interaction. Therefore, the migration which occurs with retention of configuration is symmetry-allowed.



Thermally allowed [1,5] shift of carbon:
supra-supra with retention of configuration

The antarafacial migration with respect to both the π-system and the carbocation, i.e., the *antara-antara* shift of alkyl cation is, although symmetry-allowed, geometrically not feasible.

Photochemical reaction In photochemical [1,5] shift of carbon, it is ψ_4^* (the excited state HOMO) of 2,4-pentadienyl anion which interacts with the LUMO of alkyl cation. Thus, for bonding interaction, *supra-antara* shift occurs and there is inversion of configuration at the migrating group.


Excited state HOMO of 2,4-pentadienyl anion
$h\nu$
ψ_4^*
R^1
R^2
R^3
C
LUMO of alkyl cation
(Inversion of configuration)

Photochemically allowed [1,5] shift of carbon:
supra-antara with inversion of configuration

Although the *antara-supra* shift of alkyl cation is symmetry-allowed, it is geometrically not feasible.

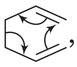
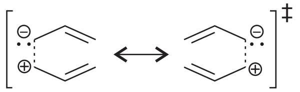
[The stereochemistry of [1,3] and [1,5] sigmatropic shift of hydrogen or carbon may also be explained by considering these as a carbanion shift across a cationic π-system or as a radical shift across a radical π-system.]

8.4.3 Woodward–Hoffmann Selection Rules for [*i, j*] Sigmatropic Shift (where *i* = 1)

	Order (i, j)	*Suprafacial* with respect to the π-system		Antarafacial with respect to the π-system	
H-shift		Thermal	Photochemical	Thermal	Photochemical
	$4n$ [1,3] shift	Forbidden	Allowed	Allowed	Forbidden
	$(4n + 2)$ [1,2] or [1,5] shift	Allowed	Forbidden	Forbidden	Allowed
Alkyl shift	$4n$ [1,3] shift	Allowed (inversion)	Allowed (retention)		
	$(4n + 2)$ [1,2] or [1,5] shift	Allowed (retention)	Allowed (inversion)		

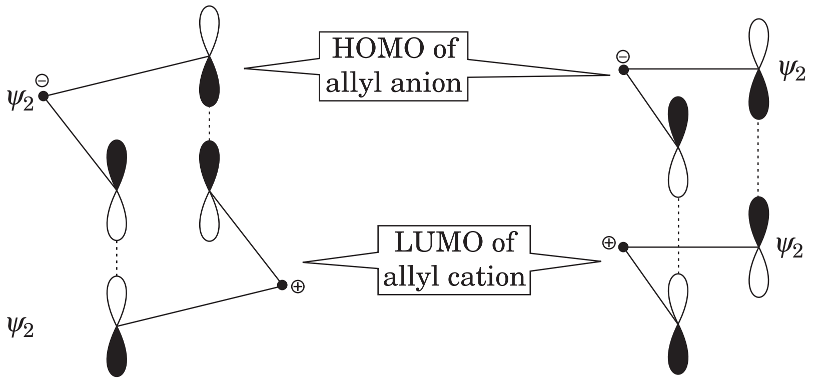
8.4.4 FMO Rationalization for [3,3] Sigmatropic Rearrangement

The transition state for [3,3] sigmatropic rearrangement can be visualized as the interactions of two allylic systems, one a cation and one an anion.

For , the transition state may be known as: 

The frontier orbitals involved are the HOMO of the anion and the LUMO of the cation, which are, in fact, the same MO (ψ_2) of the allyl system. The two MOs involved achieve bonding overlap when the [3,3] sigmatropic rearrangement occurs suprafacially on both the components. Because of symmetry allowed *supra-supra* interaction, the reaction is relatively facile thermally. [A reaction that is antarafacial on both the π-system is also allowed by orbital symmetry, but one that is suprafacial on one component and antarafacial on the other is forbidden. However, the former one is geometrically not feasible.]

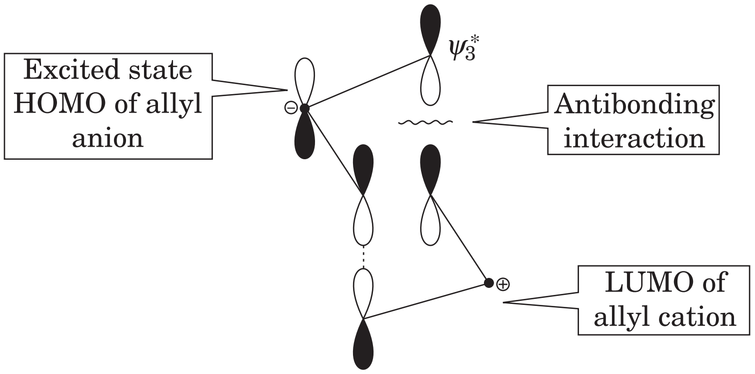
Althrough a chair-like as well as a boat-like transition state may be envisaged allowing *supra-supra* interaction, the reaction takes place through the more stable (low energy) chair-like transition state preferably.



(chair-like T.S.) (Boat-like T.S.)

Thermally allowed *supra-supra* interaction

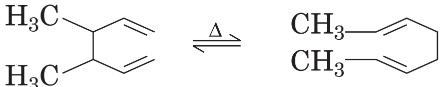
When irradiated, promotion of one electron from HOMO to the LUMO of allyl anion takes place. Therefore, ψ_3^* is now the HOMO of allyl anion which interacts with the LUMO (ψ_2) of allyl cation. Now, an orbital analysis shows that there is one antibonding interaction. Thus, the reaction is photochemically forbidden.



Photochemically forbidden *supra-supra* interaction

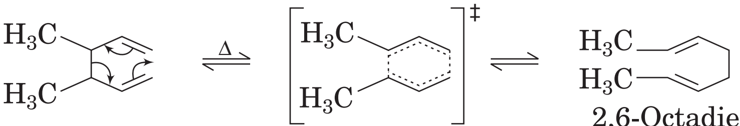
8.4.5 Cope Rearrangements

One of the best known types of [3,3] sigmatropic rearrangement is the *Cope rearrangement*. When 1,5-dienes are heated, they undergo isomerization. For example:



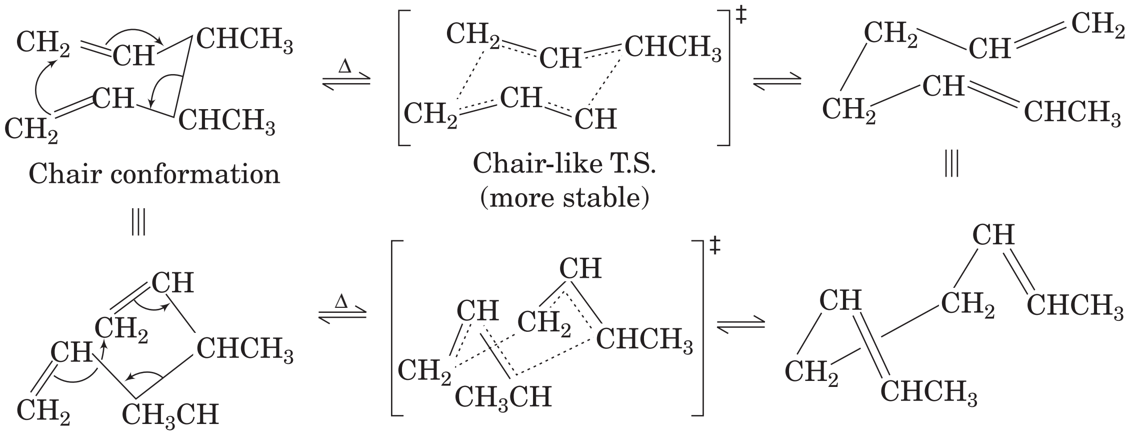
3,4-Dimethyl-1,5-hexadiene 2,6-Octadiene

Mechanism of the reaction The reaction is concerted (the cleavage of C-3—C-4 bond is synchronous with the formation of C-1—C-6 bond) and proceeds through a six-membered cyclic transition state.



3,4-Dimethyl-1,5-hexadiene T.S. (aromatic) 2,6-Octadiene

The reaction actually takes place through a chair-like transition state because it is more stable than a boat-like transition state to the extent of 25 kJ/mol.



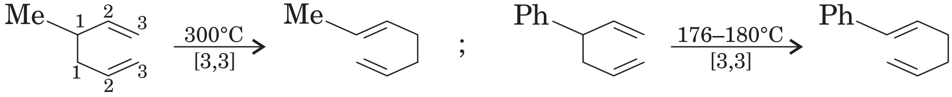
Chair conformation

Chair-like T.S. (more stable)

Boat conformation

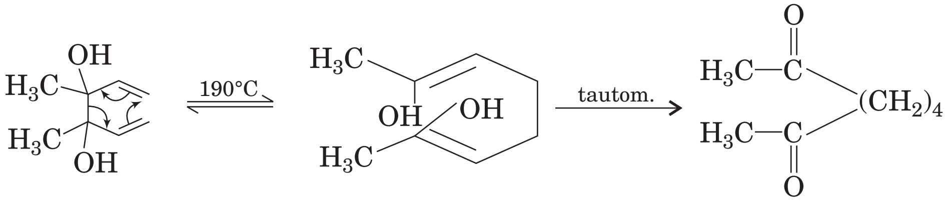
Boat-like T.S. (less stable)

The temperature needed to bring about the reaction depends on the nature of the substituents present. A conjugating group like CH_3CO—, Ph, etc. lowers the energy of the transition state and the rearrangement takes place at a relatively low temperature.

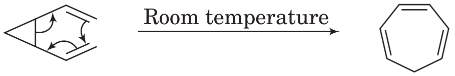


Some relevant topics are discussed below:

(a) An interesting variation of the cope rearrangement is the oxy Cope rearrangement. In this type of reaction, an enol is formed initially. Tautomerization of the enol into the corresponding carbonyl compound is a very favourable equilibrium that drives the reaction to completion. For example:



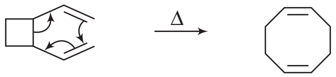
(b) If the C—C σ-bond which breaks in the reaction is a part of a small ring, the rearrangement takes place rapidly at a lower temperature to form a strain-free product. For example:



A molecule containing a strained three-numbered ring

Strain-free molecule

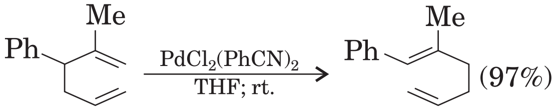
;



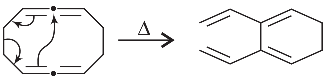
A molecule containing a strained four-membered ring

Strain-free molecule

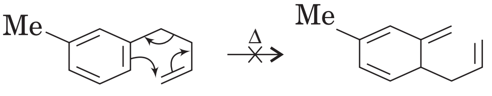
(c) A major disadvantage of the cope rearrangement from preparative point of view is the high reaction temperature. The rearrangement may, however, be carried out at a lower temperature in the presence of a catalyst like $PdCl_2$, *bis* benzonitrile. For example:



(d) The 1,5-diene unit may present inside a ring or may be a part of allenic system. For example:



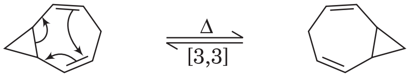
(e) The reaction does not take place when one of the double bonds is a part of an aromatic ring and this is due to high loss of resonance energy, i.e. stabilization in the product. For example:



Aromatic (more stable)

Nonaromatic (less stable)

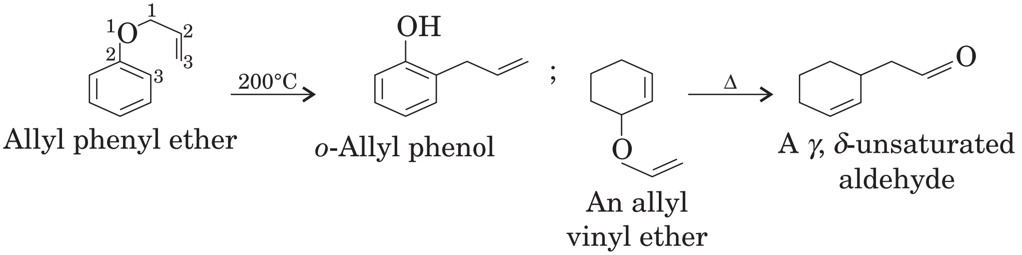
(f) A reaction in which the substrate and the product have the same structure is known as a degenerate reaction. Regeneration of homotropilidene from homotropilidine is an example of a degenerate cope rearrangement.



Homotropilidine Homotropilidine

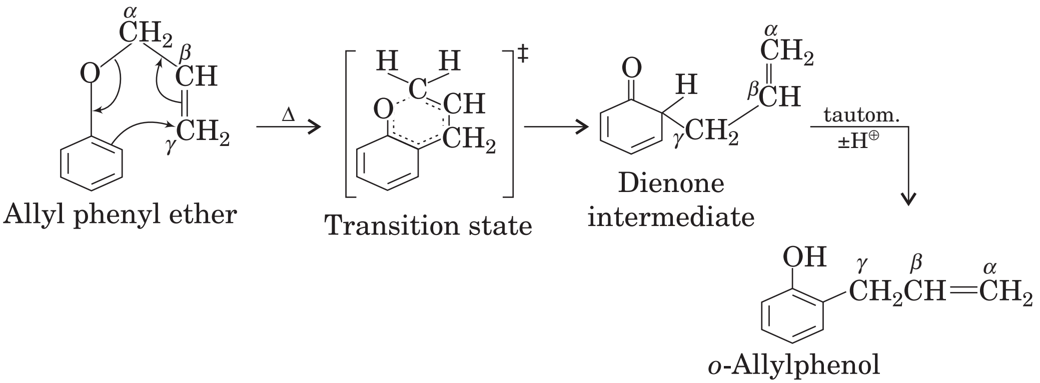
8.4.6 Claisen Rearrangements

This well studied [3,3] sigmatropic rearrangement is very much similar to the cope rearrangement except that a C—O σ-bond is broken instead of a C—C σ-bond. In this rearrangement, allyl aryl ethers and allyl vinyl ethers undergo thermal isomerization to give allyl phenols and γ, δ-unsaturated carbonyl compounds, respectively. For example:



Allyl phenyl ether; *o*-Allyl phenol; An allyl vinyl ether; A γ, δ-unsaturated aldehyde

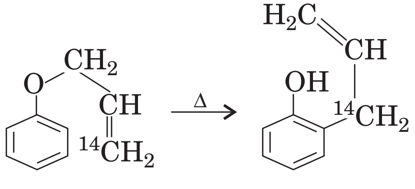
Mechanism of the reaction The reaction proceeds through a concerted pathway involving a six-membered cyclic transition state. The bond between the γ-carbon of the allyl group and the *ortho*-position of the benzene ring forms at the same time that the carbon-oxygen bond of allyl phenyl ether breaks. The product of the rearrangement is an unstable cyclohexadienone intermediate that readily tautomerizes to give *o*-allylphenol.



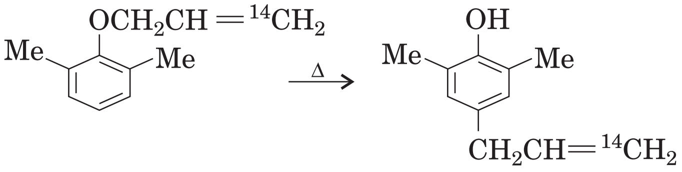
Allyl phenyl ether; Transition state; Dienone intermediate; *o*-Allylphenol

Some relevant topics are discussed below:

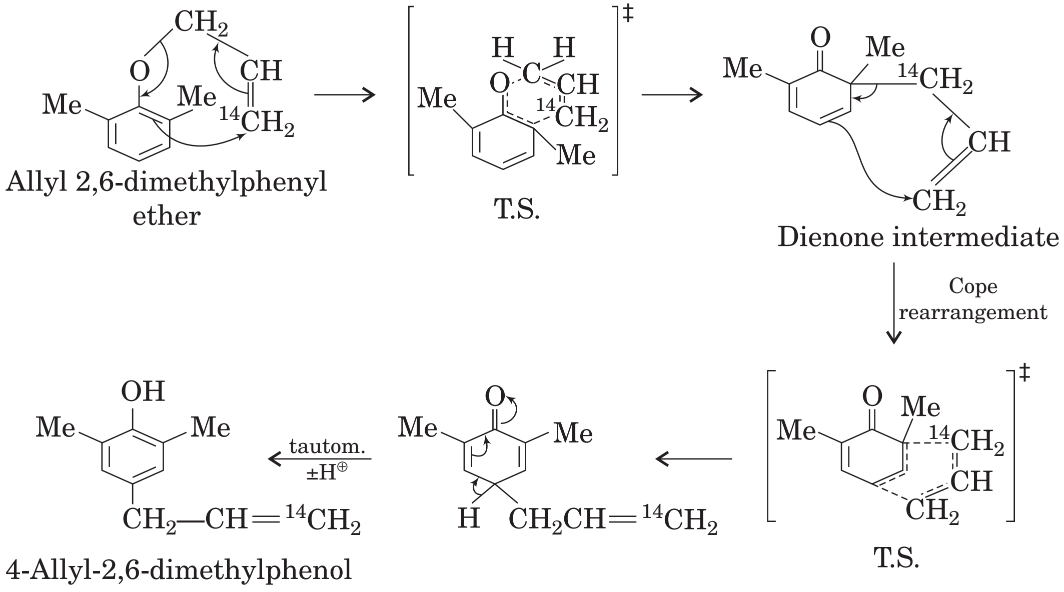
(a) When allyl phenyl ether in which the allyl group is labelled with ^{14}C at the γ-carbon atom is heated, the rearrangement product is found to contain the labelled carbon bonded to the ring. The allylic group is, therefore, end-interchanged during the rearrangement. This observation is in agreement with the intramolecular cyclic mechanism.



(b) The allyl group migrates to the *para*-position if both the *ortho*-positions are blocked (*para*-Claisen rearrangement). For example:



In the rearrangement product of the ^{14}C labelled ether, the labelled carbon is not found to be bonded to the ring. This observation can only be explained if the rearrangement proceeds by the following two-step process which involves double inversion of the position of ^{14}C label:



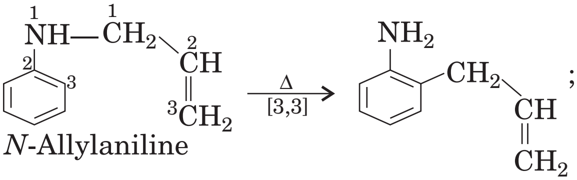
(c) The rearrangement shows large negative value of entropy. This supports the formation of a cyclic transition state which is more ordered that the substrate.

(d) Heating a mixture of two different ethers does not lead to the formation of cross-over products. The rearrangement is, therefore an intramolecular process.

All the above observations when considered together provide a strong support for a concerted mechanism involving cyclic transition state.

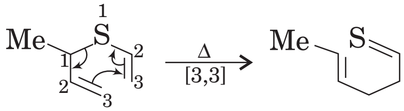
(e) This isomerization occurs because *C*-alkylation of phenols is thermodynamically more favoured over *O*-alkylation.

(f) The C—O bond of the ether may be replaced by the C—N or C—S bond, i.e., allyl aryl amines or allyl vinyl sulphides may also undergo thermal rearrangement. An allenic product may be obtained when the allyl group is replaced by a propergyl group. For example:

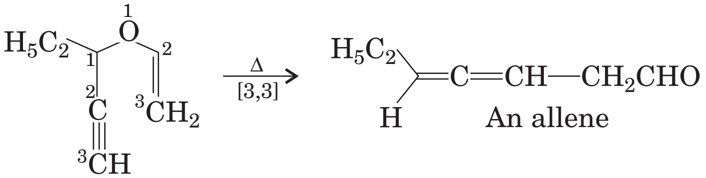


N-Allylaniline

;



An allyl vinyl sulphide

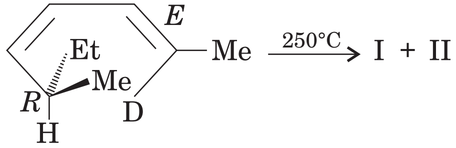


An allene

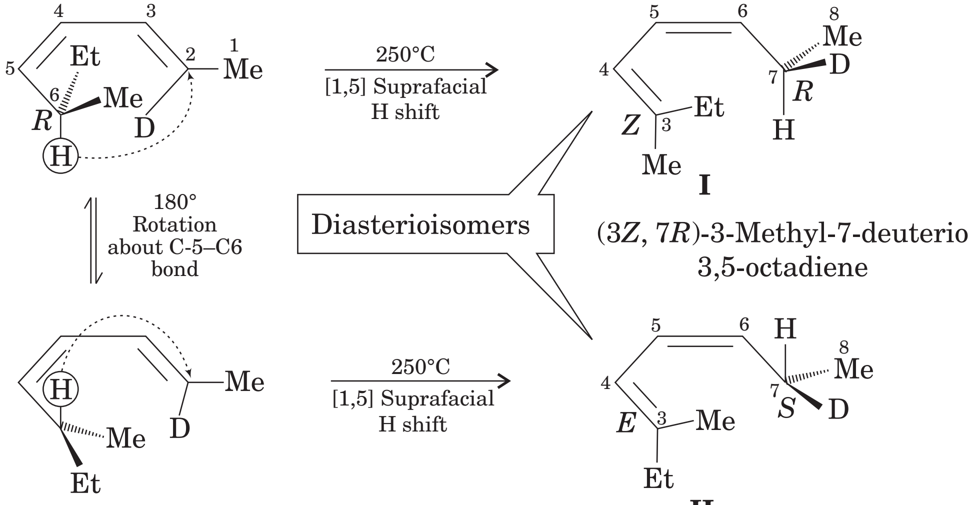
A propergyl vinyl ether

SOLVED PROBLEMS

1. Predict the diastereoisomeric products and explain the stereochemical course involved in the following sigmatropic reaction:



Solution The diene undergoes [1,5] H shift in symmetry allowed suprafacial fashion from each of the conformational isomers to give a mixture of (3*Z*, 7*R*)- and (3*E*, 7*S*)-3-methyl 7-deuterio-3,5-octadiene (two diastereoisomers). Since the migration is suprafacial, the absolute configuration of the chiral centre of the (3*Z*)-isomer is *R* and that of (3*E*)-isomer is *S*.



I

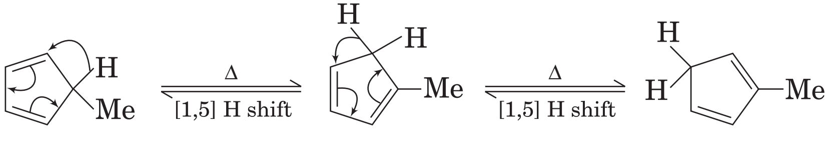
(3*Z*, 7*R*)-3-Methyl-7-deuterio
3,5-octadiene

II

(3*E*, 7*S*)-3-Methyl-7-deuterio
3,5-octadiene

2. **5-Methyl-1,3-cyclopentadiene on heating with maleic anhydride produces a mixture of three isomeric products. Explain this observation.**

Solution When 5-methyl-1,3-cyclopentadiene is heated, it undergoes a facile thermally allowed suprafacial [1,5] H shift to give a mixture of three isomeric methyl substituted cyclopentadienes. These dienes then undergo the Diels–Alder reaction with maleic anhydride to produce a mixture of three isomeric adducts.

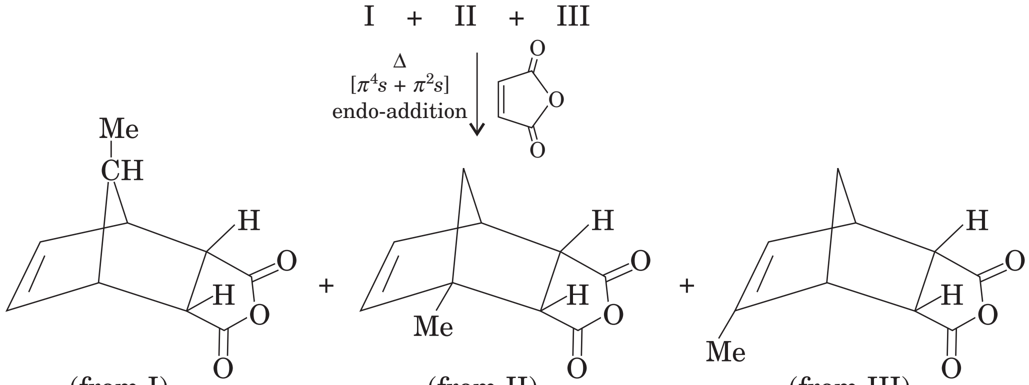


5-Methyl-1,3-cyclopentadiene
I

1-Methyl-1,3-cyclopentadiene
II

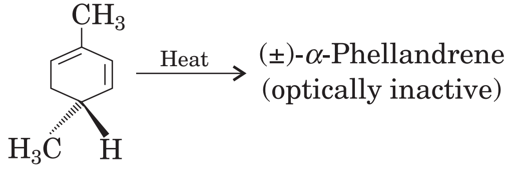
2-Methyl-1,3-cyclopentadiene
III

Now,



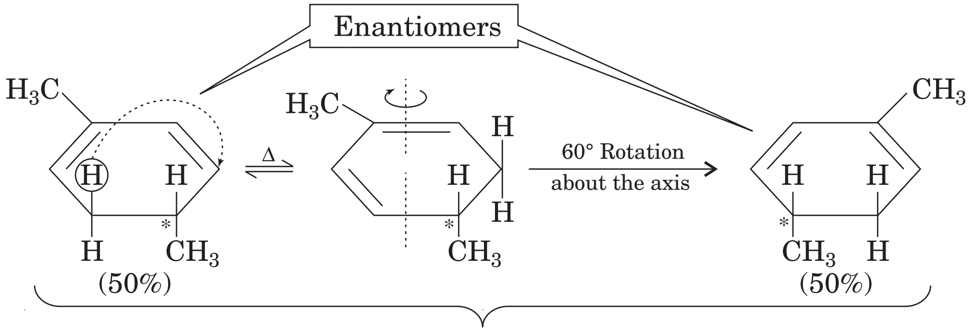
(from I) (from II) (from III)

3. **When the following enantiomer of α-phellandrene is heated, it undergoes racemization. Account for this observation.**



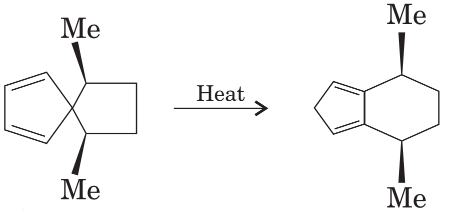
α-Phellandrene
(optically active)

Solution When this enantiomer of α-phellandrene is heated it undergoes reversible suprafacial thermally allowed [1,5] H shift. The chiral centre is not involved in this racemization process.



(±) or *rac*-α-Phellandrene (optically inactive)

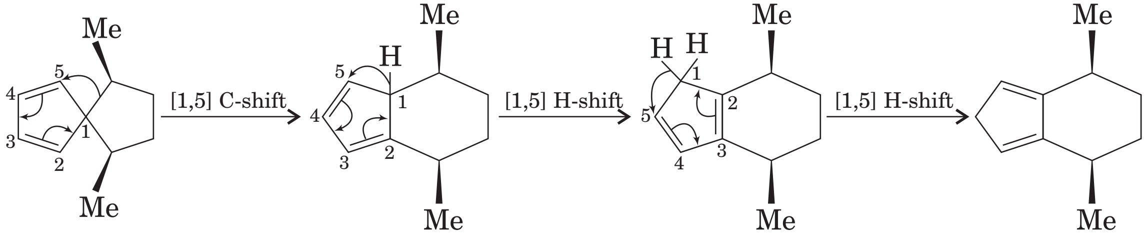
4. Explain the following sigmatropic rearrangement:



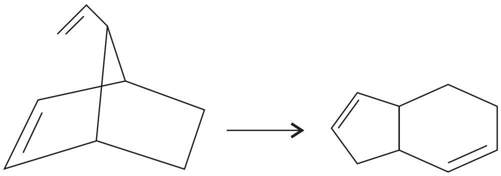
A spirane

A bicyclic compound

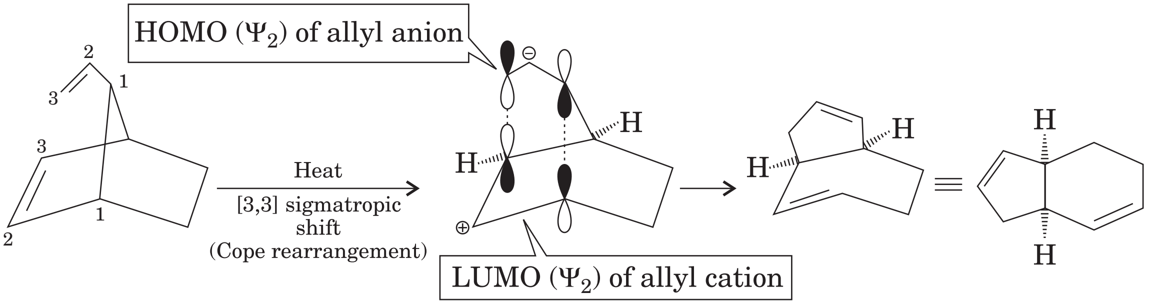
Solution The siprane undergoes thermal isomerization to give a bicyclic compound with retention of configuration. Therefore, this conversion must involve a [1,5] sigmatropic thermally allowed suprafacial migration of carbon followed by two [1,5] thermally allowed suprafacial (with respect to the diene system) migration of hydrogen. This may be shown as follows:



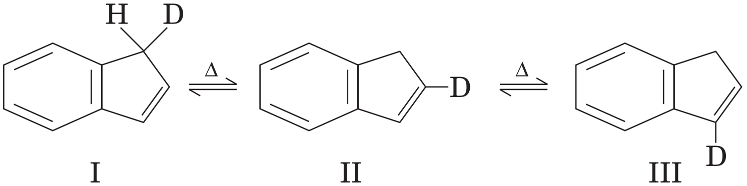
5. Classify the following pericyclic reaction as [*i*, *j*] sigmatropic rearrangement, and indicate whether it is thermally or photochemically allowed:



Solution It is a [3,3] sigmatropic rearrangement because both ends of the σ-bond move to new positions relative to their original point of attachment. There will be a bonding interaction if the HOMO of allyl anion (ψ_2) interacts with the LUMO of allyl cation (ψ_2) suprafacially with respect to both the components. That is, this rearrangement is thermally allowed. Under photochemical condition, the frontier orbitals are the excited state HOMO of allyl anion (ψ_3^*) and the ground state LUMO of allyl cation (ψ_2). There will be an antibonding interaction if they approach suprafacially, i.e., suprafacial interaction is not photochemically allowed. However, there will be bonding interaction if one of the components interact antarafacially. However, the antarafacial interaction leads to an unstable (high energy) transition state and so, the reaction does not take place through this pathway.

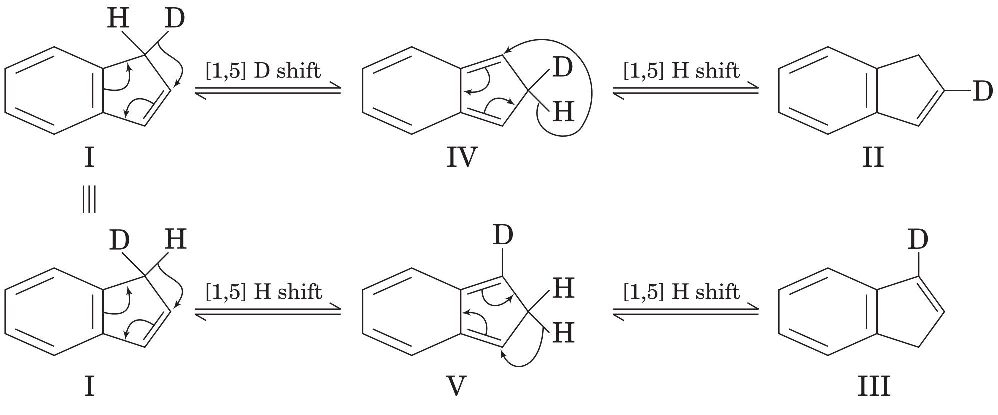


6. When 3-deuterioindene (I) is heated, scrambling of deuterium takes place among all the three non-aromatic positions.



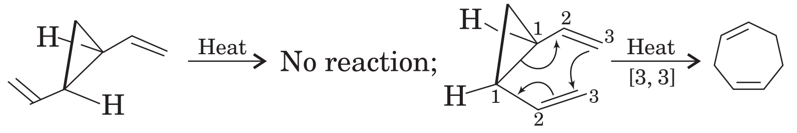
I II III

Solution Although the [1,3] sigmatropic shift of H in which the π-system behaves as the antarafacial component is symmetry allowed, it does not take place because of steric reason and therefore, the formation of the isomer II cannot be explained on the basis of [1,3] shift. Scrambling of D to all the three non-aromatic positions may be rationalized by a [1,5] shift of H or D involving benzene *p* orbitals. A [1,5] shift of D produces the unstable non-aromatic intermediate IV which then transfers H by [1,5] shift to yield II. Again, a [1,5] shift of H produces the unstable non-aromatic intermediate V which in turn undergoes [1,5] H shift to yield III.



7. **The *cis*-isomer of 1,2-divinylcyclopropane undergoes Cope rearrangement whereas the *trans*-isomer does not. Explain this observation and discuss the stereochemical course involved when the *cis*-isomer rearranges.**

Solution The *trans*-isomer of 1,2-divinylcyclopropane does not undergo the Cope rearrangement because the ends of the molecule, i.e., the two terminal sp^2 carbons are too far apart from each other. Since the ends of the molecule are very close to each other in the *cis*-isomer, it undergoes Cope rearrangement to yield 1,4-cycloheptadiene.

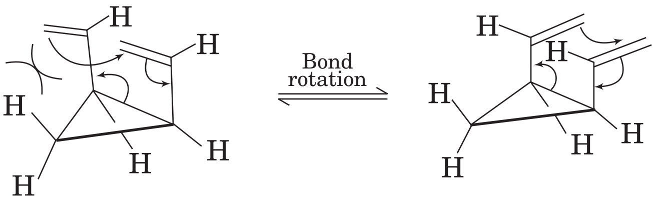


trans-1,2-Divinyl-cyclopropane

cis-1,2-Divinyl-cyclopropane

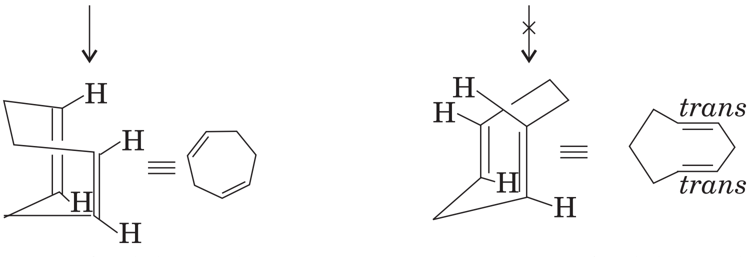
1,4-Cycloheptadiene

cis-1,2-Divinylcyclopropane can exist in two forms. One is less stable 'coiled' form in which the two vinyl groups point back towards the cyclopropane ring and are much closer to the offending *syn* hydrogen and the other is more stable 'extended' form in which the two vinyl groups are directed away from the ring, i.e., from the *syn* ring hydrogen. However, the more stable extended form cannot undergo the Cope rearrangement because it leads to the formation of a very unstable isomer of 1,4-cycloheptadiene with two *trans* double bonds. Thus, the rearrangement takes place through the less stable coiled form to produce a stable isomer of 1,4-cycloheptadiene with two *cis* double bonds.



'coiled' form of *cis*-1,2-divinylcyclopropane (less stable but suitable for rearrangement)

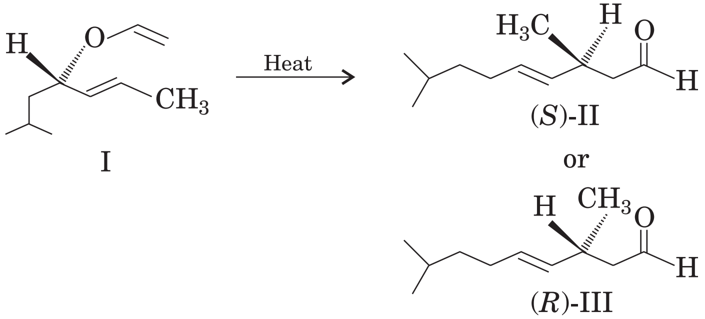
'extended' form of *cis*-1,2-divinylcyclopropane (more stable but not suitable for rearrangement)



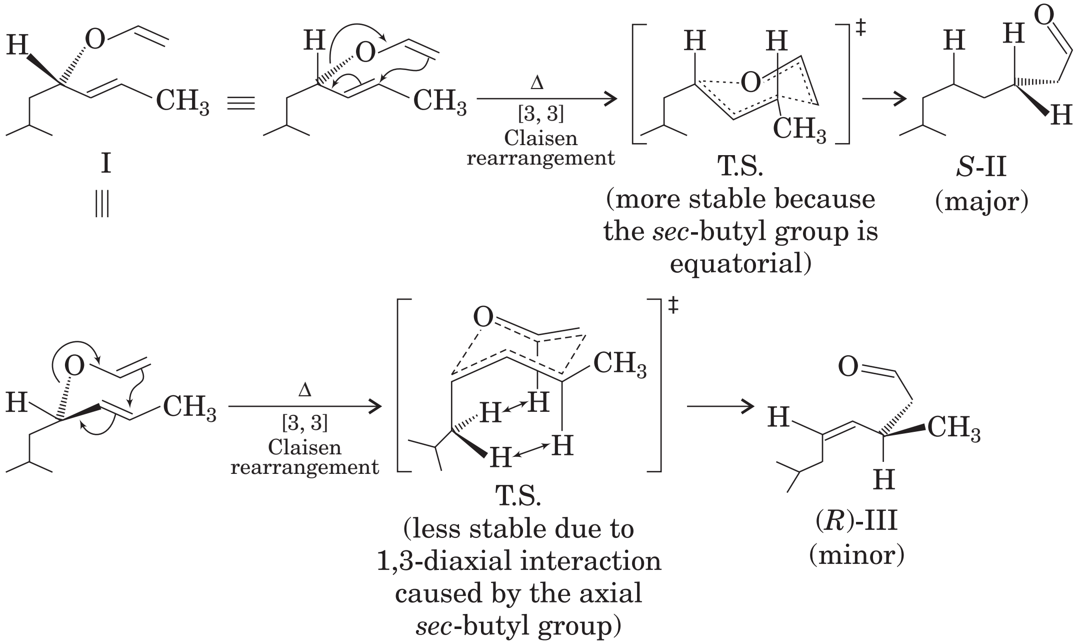
cis, *cis*-1,4-Cycloheptadiene (stable because the two double bonds are *cis*)

trans, *trans*-1, 4-Cycloheptadiene (unstable because a small ring cannot accommodate a *trans* double bond)

8. **When the allyl vinyl ether (I) is heated, one of the two enantiomeric enones (*S*) II or (*R*) III is formed as the major product (> 96%). Predict the structure of that enantiomer and explain why it is the preferred product.**



Solution The allyl vinyl ether (I) undergoes Claisen rearrangement through the chair-like transition state to yield the two enantiomeric enones as follows:



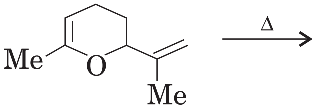
(more stable because the *sec*-butyl group is equatorial)

(less stable due to 1,3-diaxial interaction caused by the axial *sec*-butyl group)

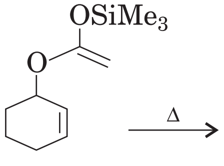
(*S*)-II is obtained as the major product to avoid the 1,3-diaxial interaction in the chair-like transition state.

9. **Predict the product and give a mechanistic rationalization for each of the following pericyclic reactions.**

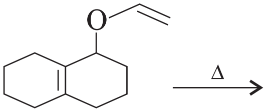
(a)



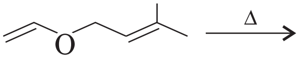
(b)



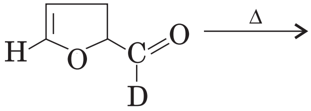
(c)



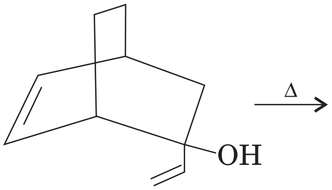
(d)



(e)

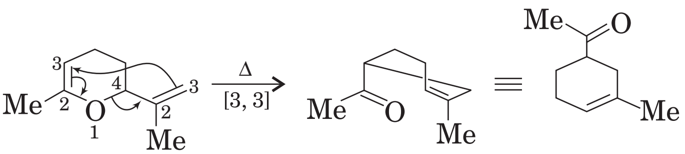


(f)

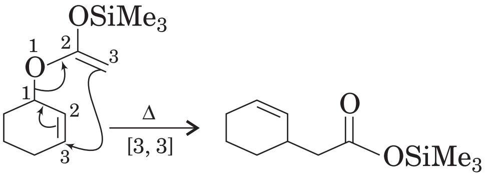


Solution

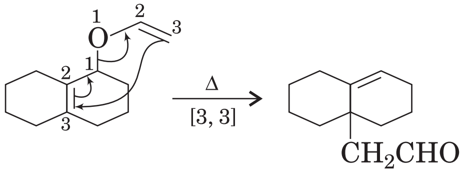
(a) This allyl vinyl ether undergoes Claisen rearrangement (a [3, 3] sigmatropic shift) to give an unsaturated ketone.



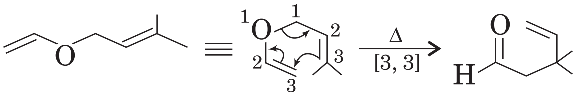
(b) This trimethylsilyl enol ether undergoes [3, 3] sigmatropic shift to give the corresponding cyclohexene derivative.



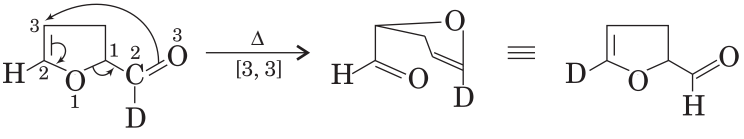
(c) When this allyl vinyl ether is heated, it undergoes Claisen arrangement to give an unsaturated aldehyde.



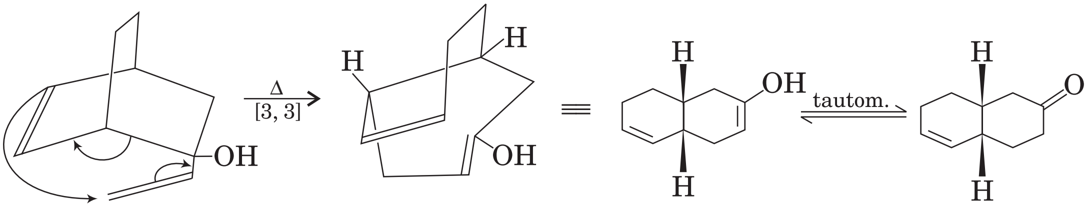
(d)



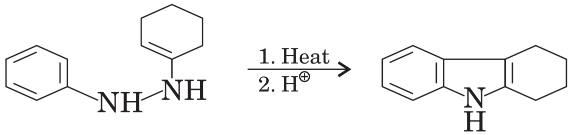
(e) This dihydrofuran undergoes [3,3] sigmatropic shift to give an isomeric compound in which the positions of D and H have been exchanged.



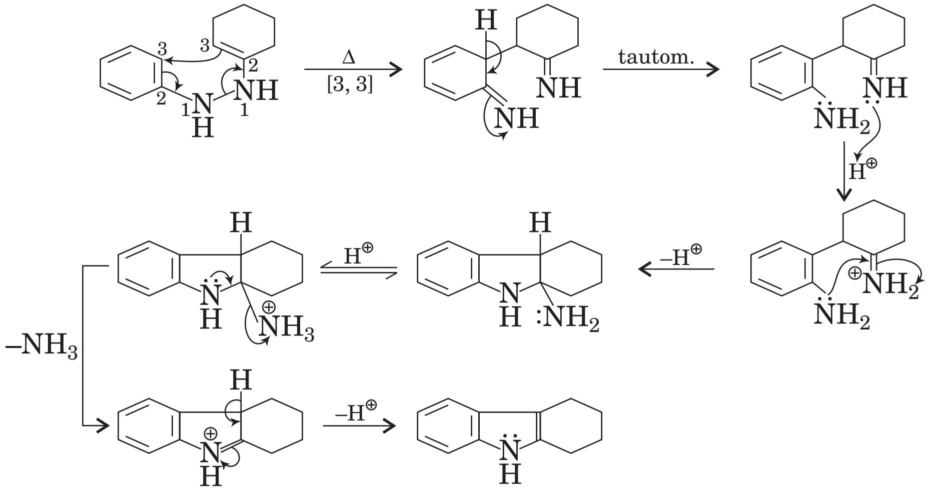
(f) This unsaturated alcohol undergoes Cope rearrangement (a [3,3] sigmatropic shift) to give an enol which readily tautomerizes to give the corresponding ketone.



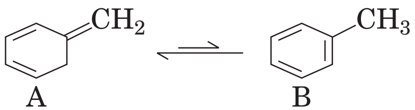
10. The following phenylhydrazine can be converted to an indole derivative by the reaction given below. Propose a reasonable mechanism for this reaction.



Solution This phenylhydrazine has the ideal structure for undergoing a [3, 3] sigmatropic rearrangement. In this process, the N—N σ-bond is broken and as highly unstable double imine is formed. When this imine is treated with acid, it is readily converted into an indole derivative. The mechanism of the reaction may be shown as follows:

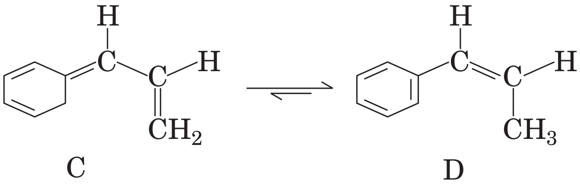


11. (a) The compound A has been prepared and is found to be stable in gas phase at 70°C. Explain why the conversion of A into B would not be expected to take place as a concerted reaction, even though the product is aromatic.



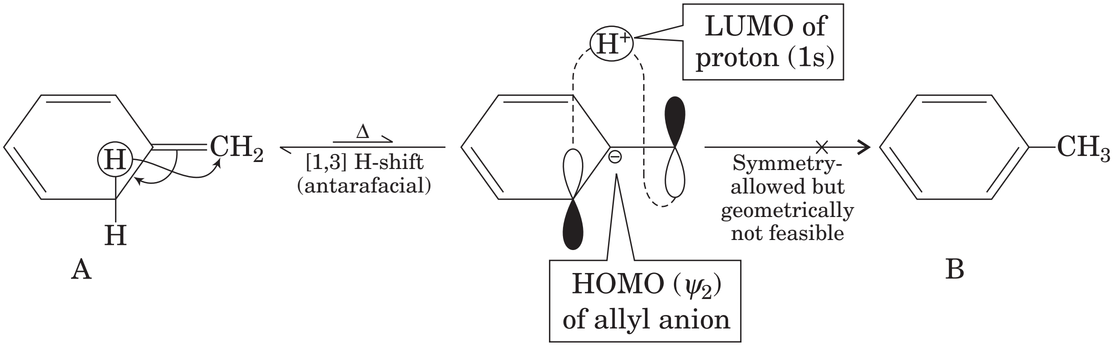
A B

(b) Explain why the conversion of C into D is expected to take place as concerted reaction.

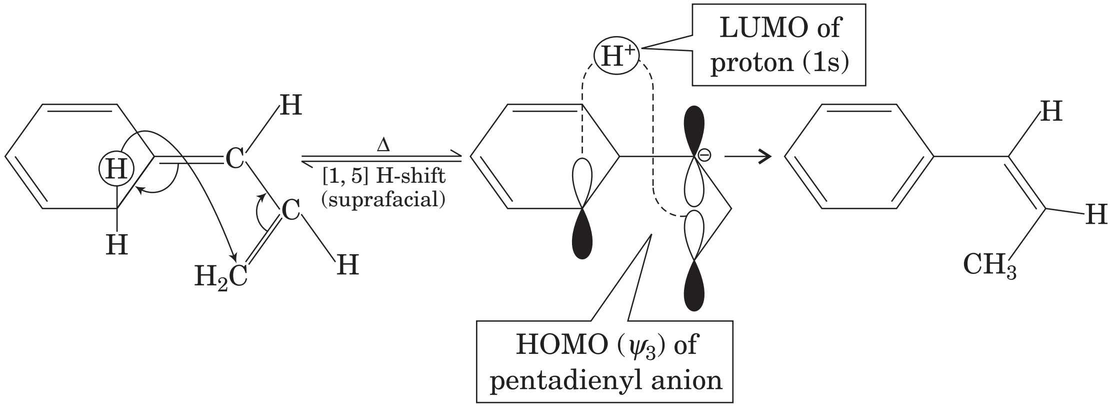


Solution

(a) The conversion of A into B requires a [1,3] sigmatropic shift of hydrogen. According to the principle of orbital symmetry, the thermal suprafacial [1,3] H-shift is forbidden but the antarafacial [1,3] H-shift is allowed. However, because of structural rigidity of A, antarafacial shift of H involves a highly strained and unstable transition state which is not possible to attain in a concerted reaction. For this reason, conversion of A into B would not be expected to take place concertedly.

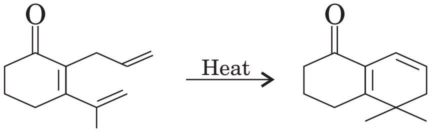

H
CH$_2$
H
A
Δ
[1,3] H-shift
(antarafacial)
H$^+$
LUMO of proton (1s)
⊖
HOMO (ψ_2) of allyl anion
Symmetry-allowed but geometrically not feasible
CH$_3$
B

(b) The conversion of C into D requires a thermal [1,5] H-shift. Since the suprafacial [1,5] H-shift is symmetry-allowed, the conversion takes place concertedly.

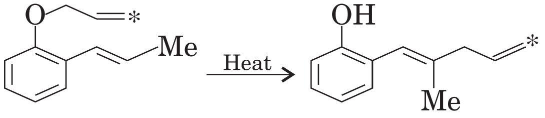


12. Suggest a suitable mechanism for each of the following pericyclic reactions:

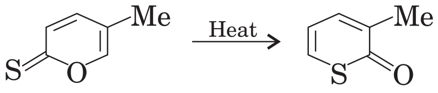
(a)



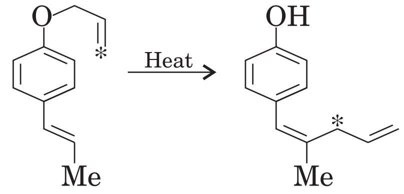
(b)



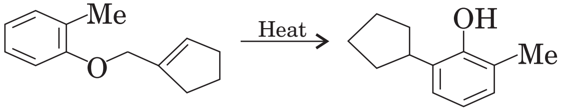
(c)



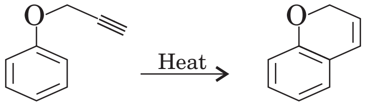
(d)



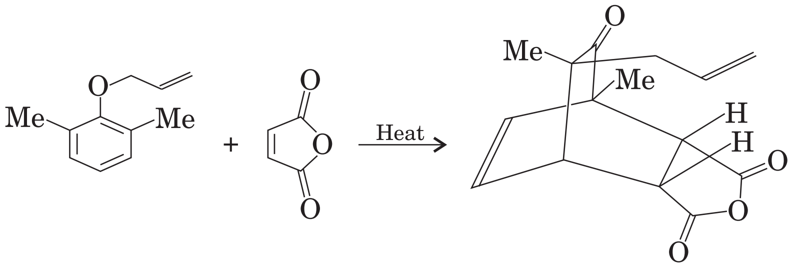
(e)



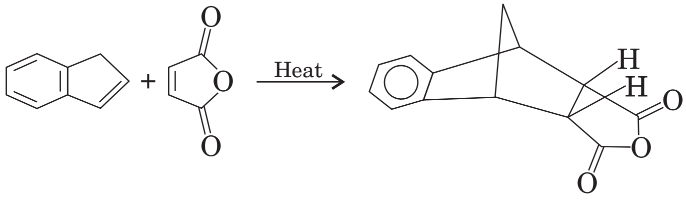
(f)



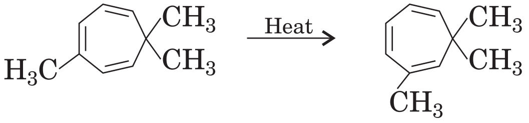
(g)



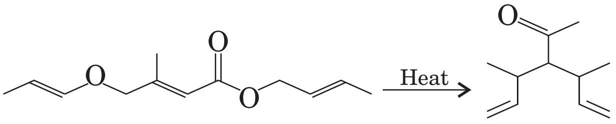
(h)



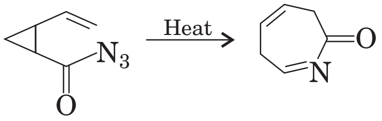
(i)



(j)

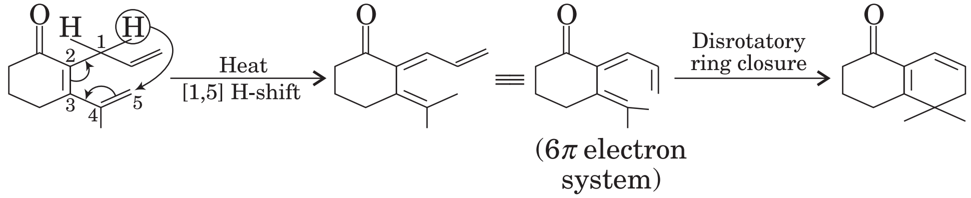


(k)

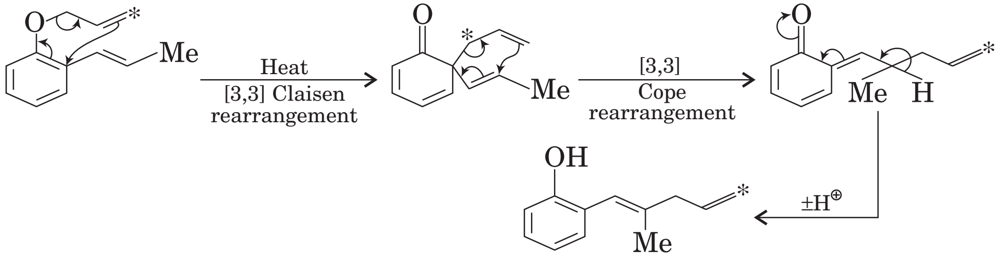


Solution

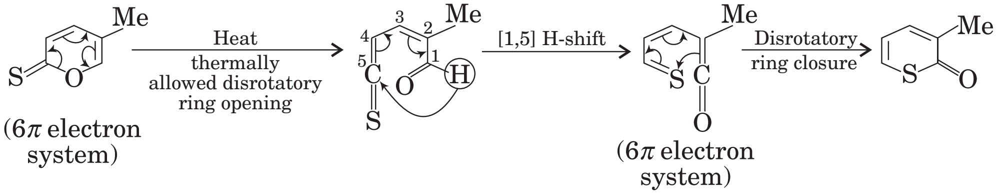
(a)



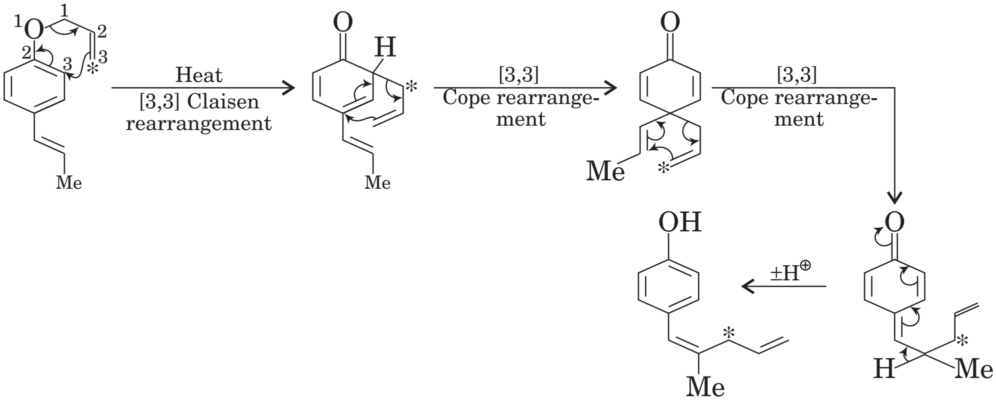
(b)



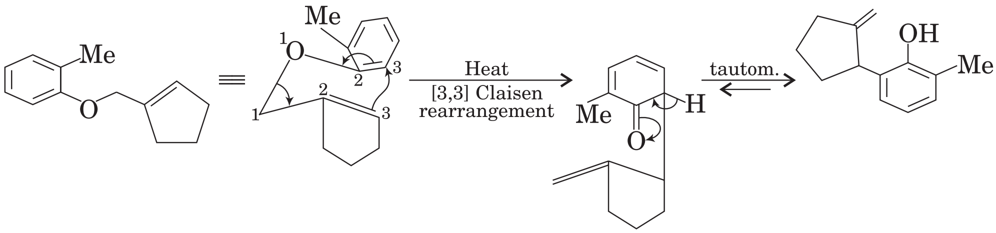
(c)



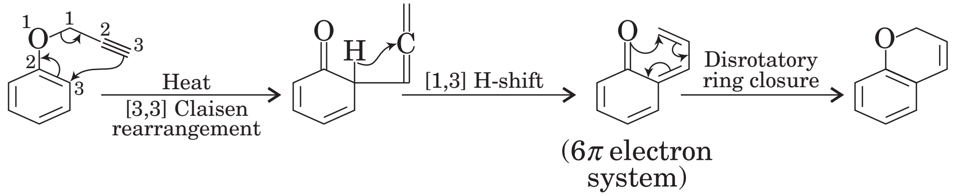
(d)


1
O
1
2
2
3
3
*
Me
Heat
[3,3] Claisen rearrangement
O
H
*
Me
[3,3] Cope rearrange-ment
O
Me
*
[3,3] Cope rearrange-ment
O
*
H
Me
±H⊕
OH
*
Me

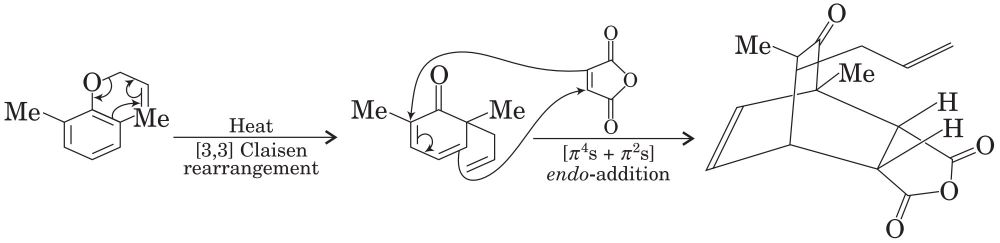
(e)



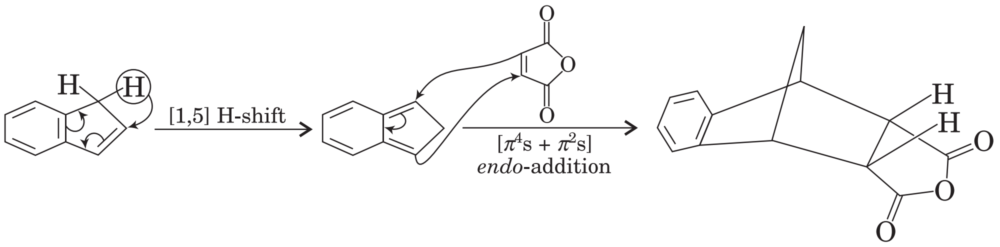
(f)


Heat
[3,3] Claisen rearrangement
[1,3] H-shift
Disrotatory ring closure
(6π electron system)

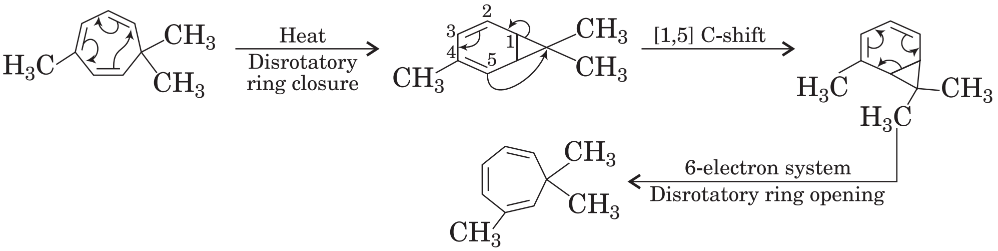
(g)


Heat
[3,3] Claisen rearrangement
[π4s + π2s]
endo-addition

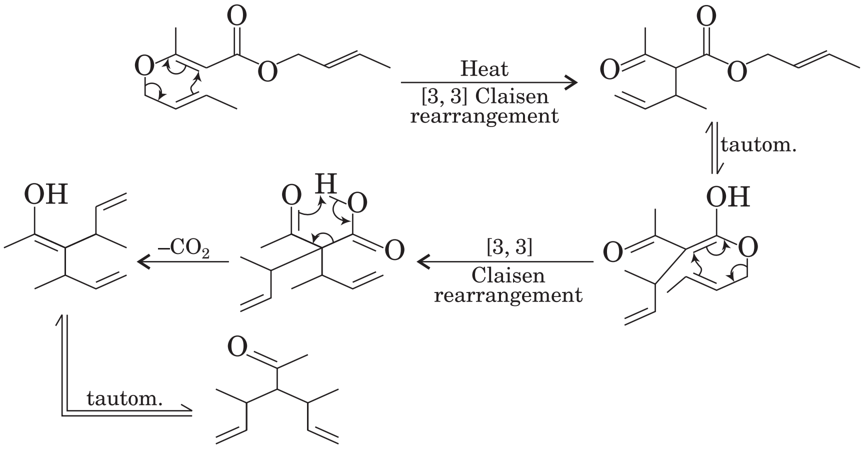
(h)

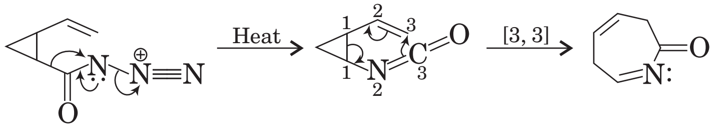

[1,5] H-shift
[π4s + π2s]
endo-addition

(i)

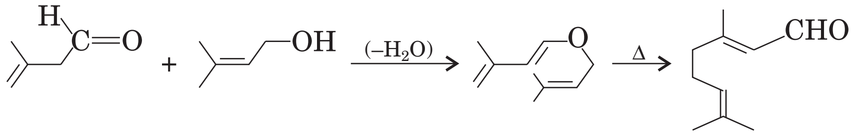

Heat
Disrotatory ring closure
[1,5] C-shift
6-electron system
Disrotatory ring opening

(j)


Heat
[3, 3] Claisen rearrangement
tautom.
[3, 3] Claisen rearrangement
–CO2
tautom.

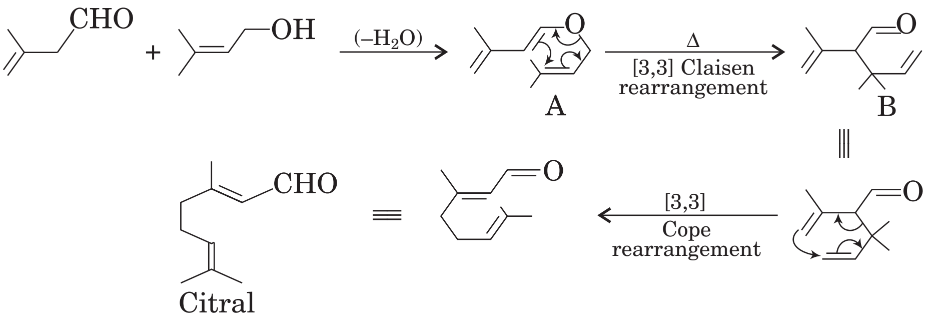
(k) 

13. Explain the formation of the terpenoid citral through the following reaction sequence via sigmatropic rearrangement:



citral

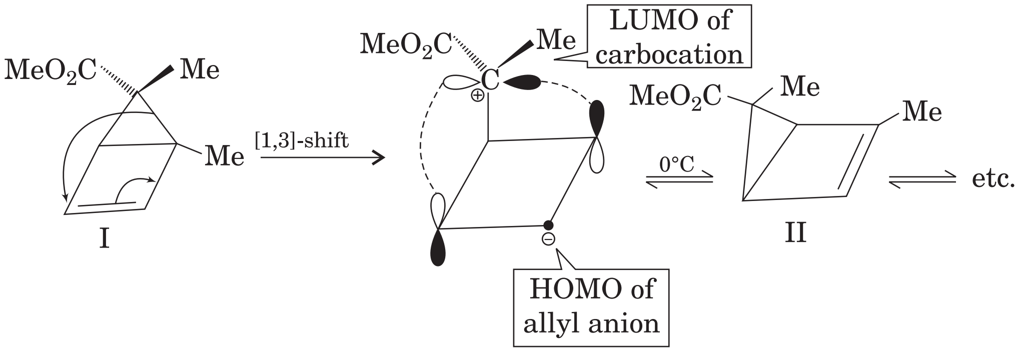
Solution When the allyl vinyl ether (A) is heated, it undergoes Claisen rearrangement to give a carbonyl compound (B) which subsequently undergoes Cope rearrangement to give citral.



14. What do you mean by 'Walk rearrangements'? Explain with a suitable example.

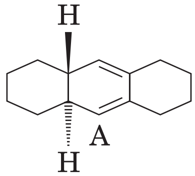
Solution In some sigmatropic rearrangements, it has been observed that cyclopropyl ring fused with a larger ring (i.e., in bicycle [n.1.0] systems) containing conjugated π-system appears to be walking around the ring in a concerted process; this type of sigmatropic rearrangements are called 'walk rearrangements'.

The migration must necessarily take place in suprafacial fashion with respect to the larger ring (on the same side as the cyclopropane ring) but may be either suprafacial or antarafacial on the migrating group so as to make the process symmetry-allowed. When the carbon migrates suprafacially, it retains its configuration but its two substituents alternate their position as *endo* and *exo*. However, when the carbon migrates antarafacially, it undergoes inversion of configuration with the result that the *endo* and the *exo* groups remain *endo* and *exo* respectively through the walking process. For example, the bicyclo [2.1.0]pentyl derivative (I) undergoes thermal [1,3] sigmatropic rearrangement to give the relatively more stable isomer (II). The orbital picture is given in the middle which is consistent with the stereochemistry, i.e., inversion at the migrating centre and retention of the *endo-exo* status of the substituents.

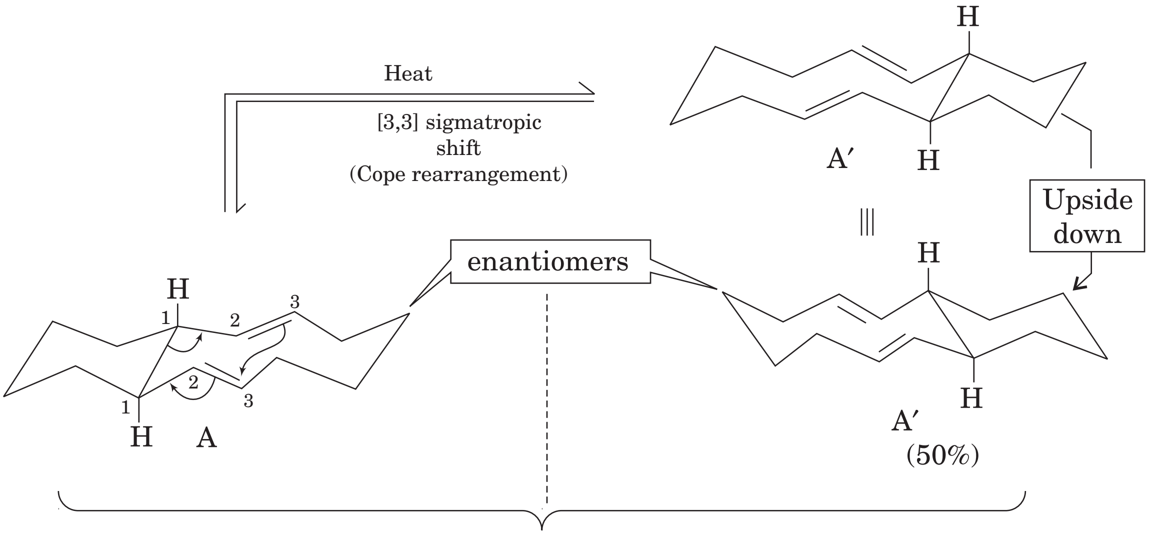


Thermally allowed [1,3] shift of carbon:
supra-antara with inversion of configuration

15. The optically active diene A racemizes on heating at 50°C. Account for this observation.

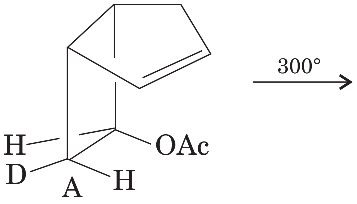


Solution This chiral diene undergoes Cope rearrangement (i.e., a [3,3] sigmatropic rearrangement) to produce its enantiomers (A′). Similarly A′ undergoes Cope rearrangement to give A. When the rates of the two transformations become equal, a racemic mixture (optically inactive) is obtained.

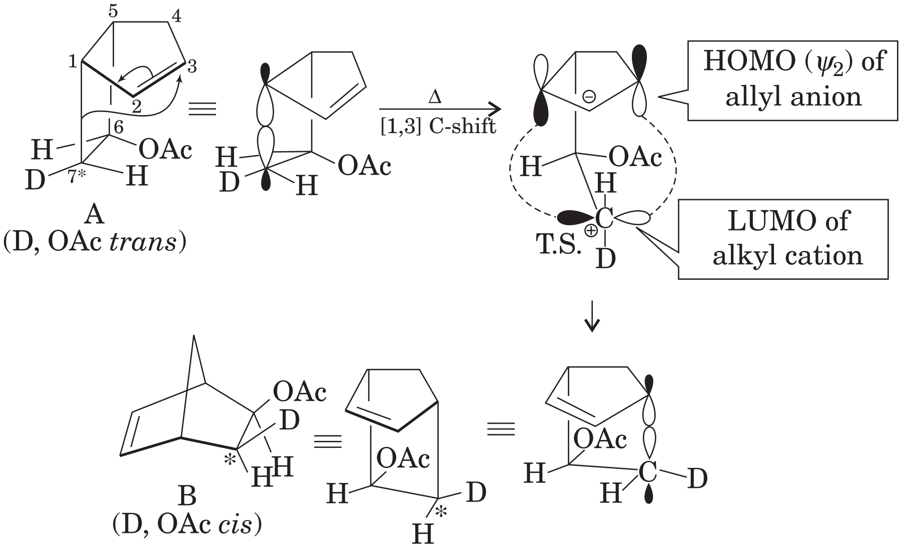


(±)
Racemic mixture

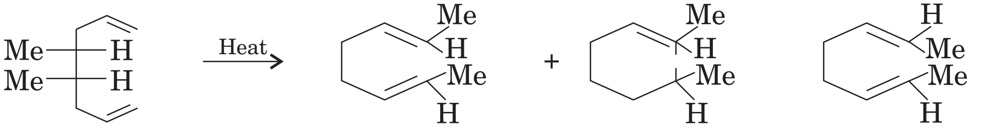
16. Predict the product in the following sigmatropic reaction and explain its formation on the basis of FMO theory:



Solution This deuterium lebelled bicyclo [3.2.0]heptene (A) undergoes thermally allowed [1,3] shift of carbon (C-7) with inversion of configuration. The LUMO of the alkyl cation (an empty *p* orbital) interacts with the HOMO (ψ_2) of an allyl anion. For bonding overlap to take place, the alkyl cation acts as the antarafacial component and the π-system acts as the suprafacial component and because of this, *exo*-norbornene (B) is formed stereospecifically.



17. Explain the formation of the products in the following reactions (Cope rearrangement):

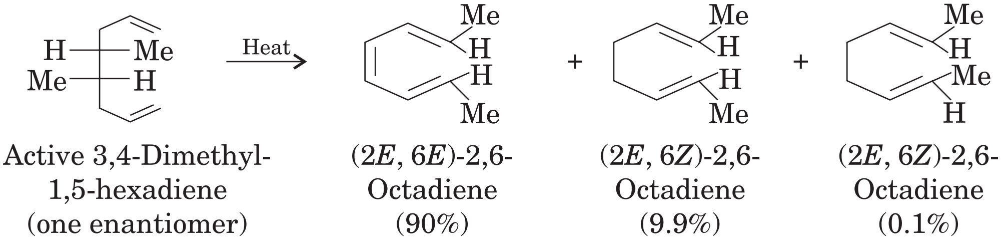


meso-3,4-Dimethyl-1,5-hexadiene

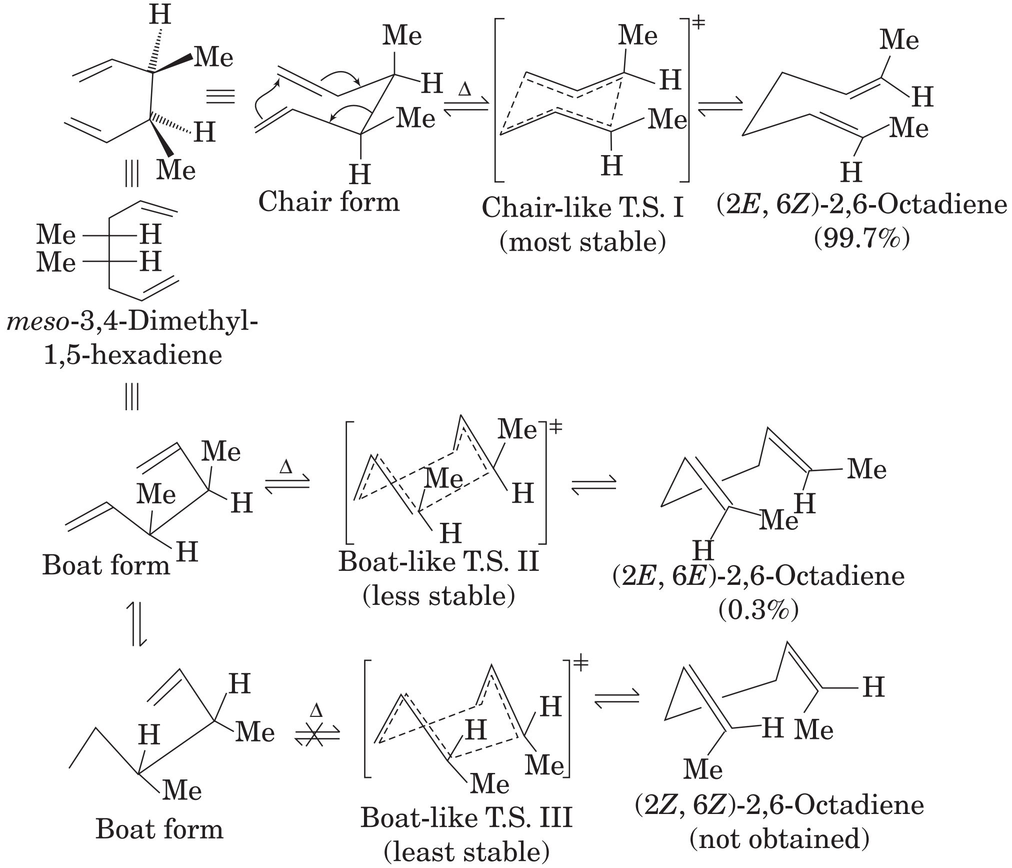
(2*E*, 6*Z*)-2,6-Octadiene (99.7%)

(2*E*, 6*E*)-2,6-Octadiene (0.3%)

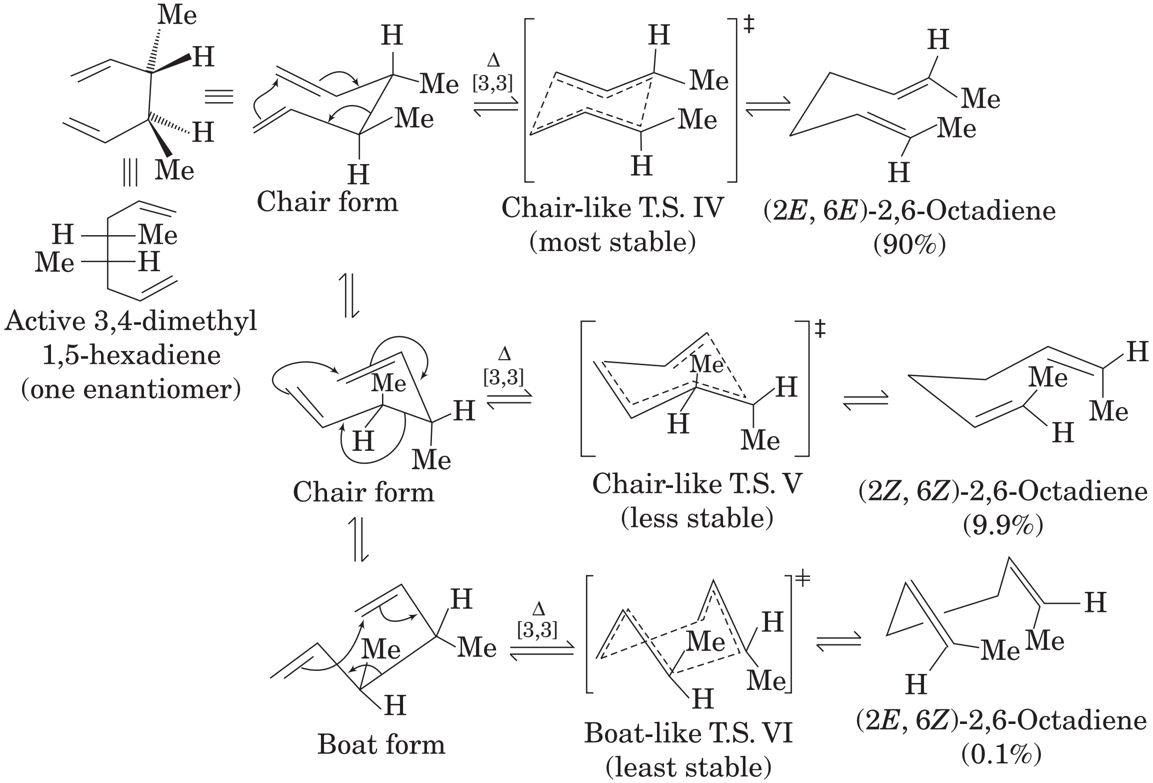
(2*Z*, 6*Z*)-2,6-Octadiene (not obtained)


H
Me
Me
H
Heat
Me
H
H
Me
+
Me
H
H
Me
+
Me
H
Me
H
Active 3,4-Dimethyl-1,5-hexadiene (one enantiomer)
(2E, 6E)-2,6-Octadiene (90%)
(2E, 6Z)-2,6-Octadiene (9.9%)
(2E, 6Z)-2,6-Octadiene (0.1%)

Solution The Cope rearrangement is highly stereoselective. The reaction proceeds preferentially through the more stable (lower E_{act}) chair-like T.S. I rather than the less stable (higher E_{act}) boat-like T.S. II and because of this, *meso*-3,4-dimethyl-1,5-hexadiene isomerizes mainly through the chair-like T.S. I to yield (2*E*, 6*Z*)-2,6-octadiene predominantly (99.7%). A very small amount of the (2*E*, 6*E*)-isomer is obtained through the boat like T.S. II. Since the boat-like T.S. III leading to the formation of (2*Z*, 6*Z*)-isomer is least stable (due to steric strain), it is not at all formed,

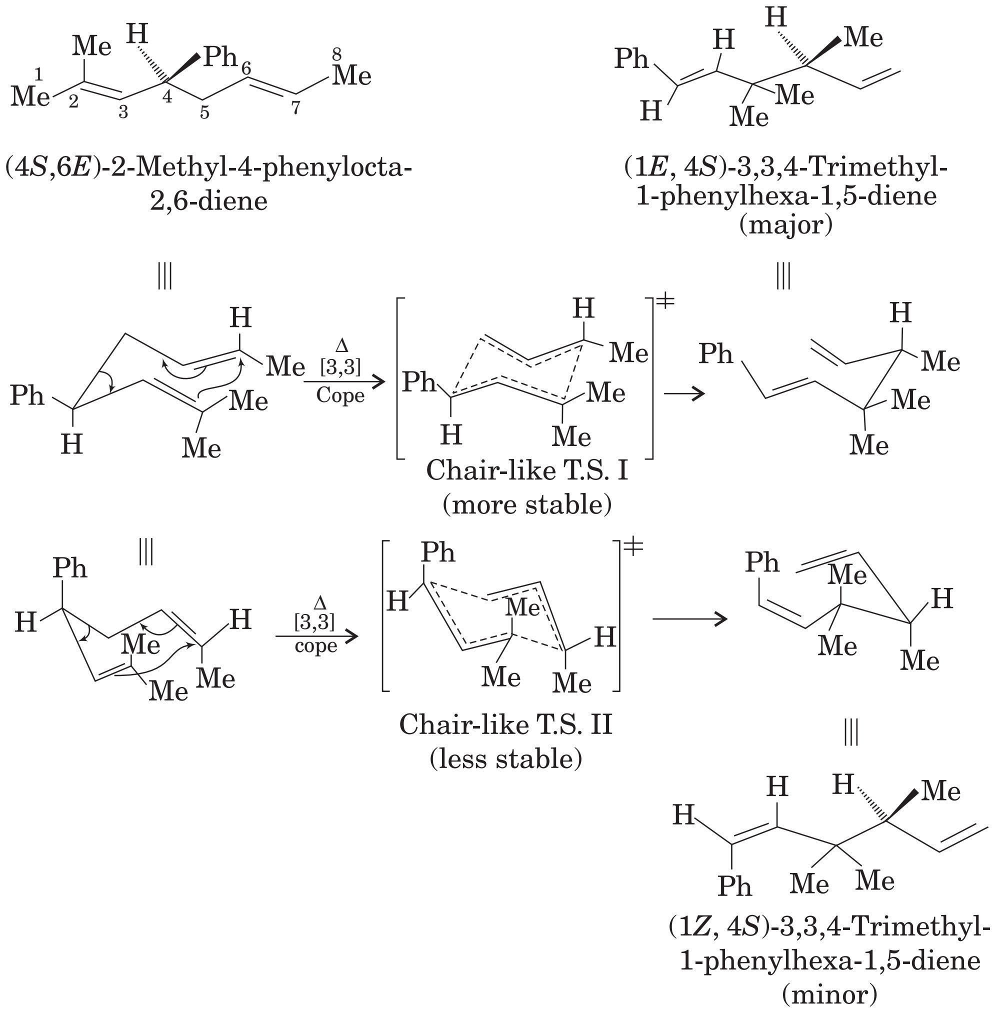

H
Me
H
Me
Me
H
Me
H
Chair form
Δ
Me
H
Me
H
‡
Chair-like T.S. I (most stable)
Me
H
Me
H
(2E, 6Z)-2,6-Octadiene (99.7%)
Me
Me
H
H
meso-3,4-Dimethyl-1,5-hexadiene
Me
Me
H
H
Boat form
Δ
Me
Me
H
H
‡
Boat-like T.S. II (less stable)
Me
H
Me
H
(2E, 6E)-2,6-Octadiene (0.3%)
H
H
Me
Me
Boat form
Δ
H
H
Me
Me
‡
Boat-like T.S. III (least stable)
H
H
Me
Me
(2Z, 6Z)-2,6-Octadiene (not obtained)

Active 3,4-dimethyl-1,5-hexadiene rearranges through the most stable chair-like T.S. IV (free from 1,3-diaxial interaction since the methyl groups are equatorial) to give (2*E*,6*E*)-2,6-octadiene predominantly (90%) and through the less stable chair-like T.S.V (which suffers from 1,3-diaxial interactions due to presence of two axial methyl groups) to yield a small amount (9.9%) of the (2*Z*,6*Z*)-isomer. A very small amount (0.1%) of the (2*E*,6*Z*)-isomer is obtained through the least stable boat like T.S. VI.


Me
H
H
Me
H
Me
Me
H
Active 3,4-dimethyl 1,5-hexadiene (one enantiomer)
H
Me
Me
H
Chair form
Δ [3,3]
H
Me
Me
H
‡
Chair-like T.S. IV (most stable)
H
Me
Me
H
(2E, 6E)-2,6-Octadiene (90%)
Me
H
H
Me
Chair form
Δ [3,3]
Me
H
H
Me
‡
Chair-like T.S. V (less stable)
H
Me
Me
H
(2Z, 6Z)-2,6-Octadiene (9.9%)
H
Me
Me
H
Boat form
Δ [3,3]
Me
H
Me
H
‡
Boat-like T.S. VI (least stable)
H
Me
Me
H
(2E, 6Z)-2,6-Octadiene (0.1%)

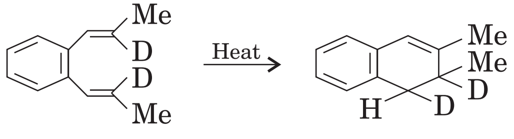
18. **When (4*S*, 6*E*)-2-methyl-4-phenylocta-2,6-diene is heated, it undergoes Cope rearrangement to give (1*E*, 4*S*)-3,3,4-trimethyl-1-phenylhexa-1,5-diene as the major product and the (1*Z*, 4*S*)-isomer as the minor product. Account for this observation.**

Solution The rearrangement takes place mainly through the more stable chair-like transition state I (only one Me group is axial) rather than the less stable chair-like transition state II (the Ph and two Me groups are axial) to yield (1*E*, 4*S*)-3,3,4-trimethyl-1-phenylhexa-1,5-diene as the major product.

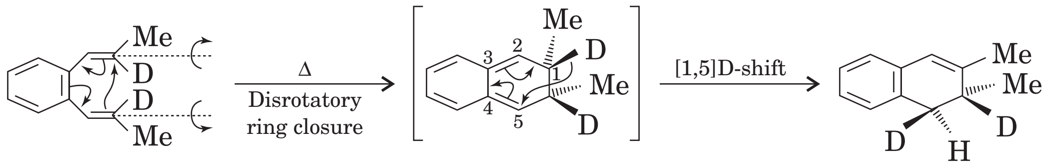


Me
H
Ph
1
Me
2
3
4
5
6
7
8
Me
(4S,6E)-2-Methyl-4-phenylocta-2,6-diene
H
Ph
H
Me
H
Me
Me
(1E, 4S)-3,3,4-Trimethyl-1-phenylhexa-1,5-diene (major)
Δ
[3,3]
Cope
Chair-like T.S. I (more stable)
Chair-like T.S. II (less stable)
cope
(1Z, 4S)-3,3,4-Trimethyl-1-phenylhexa-1,5-diene (minor)

19. Account for the following transformation and show the stereochemistry of the product:

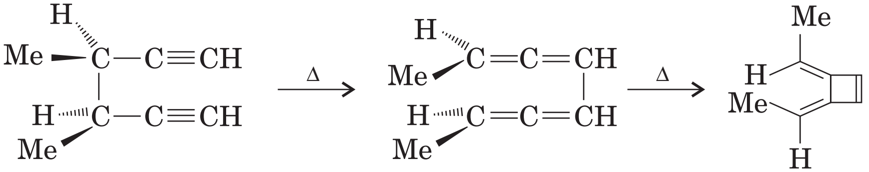


Solution This transformation involves two consecutive pericyclic reaction. A thermal six-electron electrocyclic ring closure by symmetry allowed disrotatary pathway takes place first to produce an unstable nonaromatic intermediate. The intermediate then undergoes a thermally allowed suprafacial [1,5] D-shift to give the product.

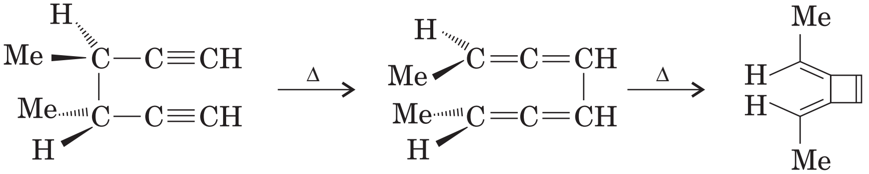


20. Explain each step in the following concerted transformations:

(a)

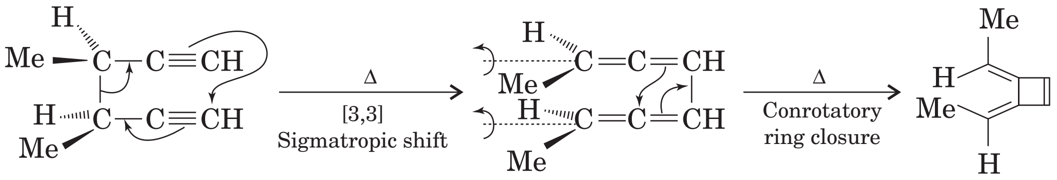


(b)

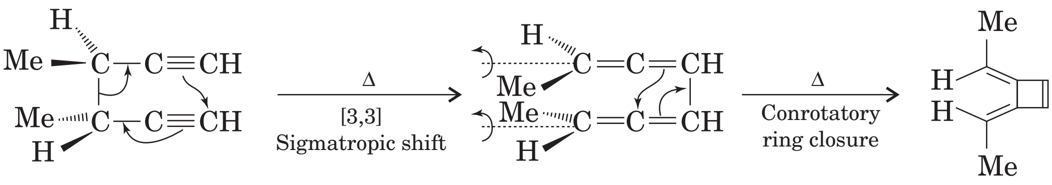


Solution

(a) The first step of this reaction sequence is a thermally allowed [3,3] sigmatropic shift involving six electrons. The second step is an electrocyclic reaction involving butadiene moiety. The structure of the product reveals that the ring closure has taken place through controtatory mode as expected according to the selection rules for the butadiene system under Δ condition.

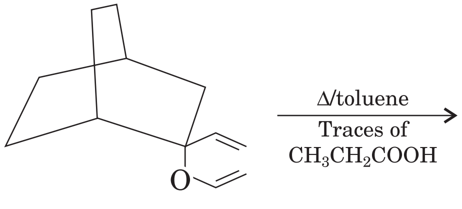


(b)

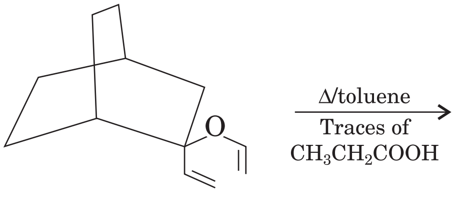


21. Write the structure of the products with stereochemistry in each case:

(a)

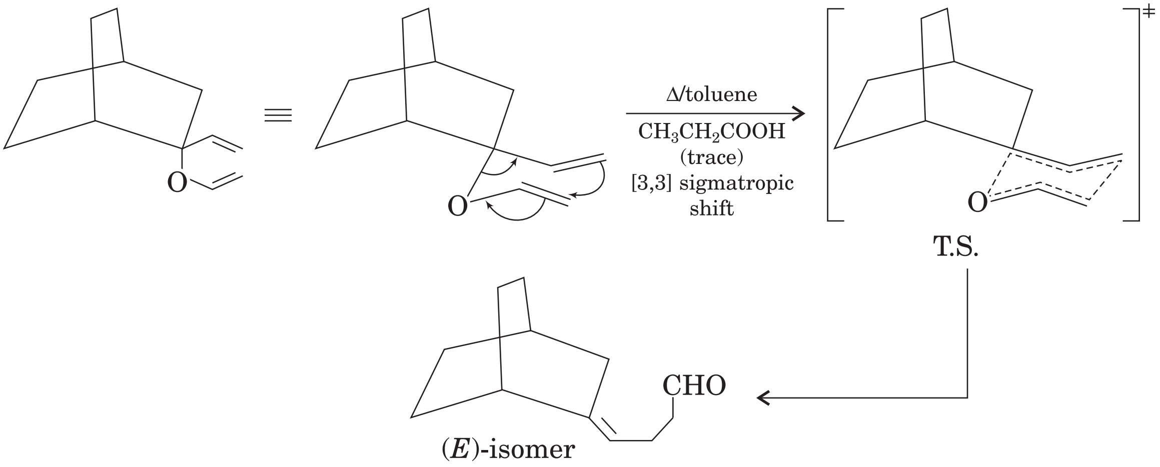


(b)

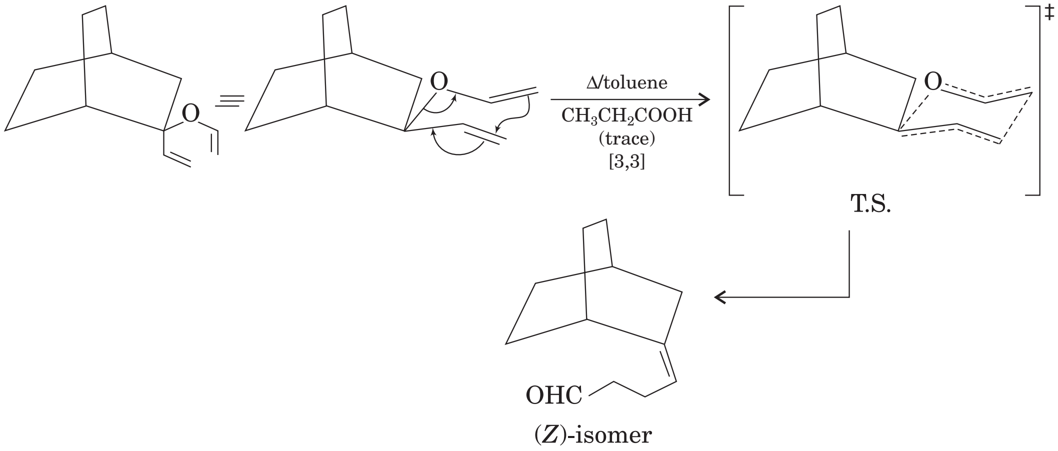


Solution

(a) This allyl vinyl ether undergoes Claisen rearrangement (a [3, 3] sigmatropic shift) through a chair-like transition state to yield the (*E*)-isomer of an unsaturated aldehyde.

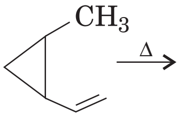


(b)

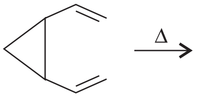


22. Predict the products of the following reactions:

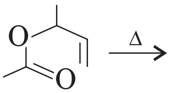
(a)



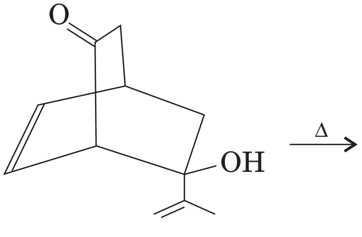
(b)



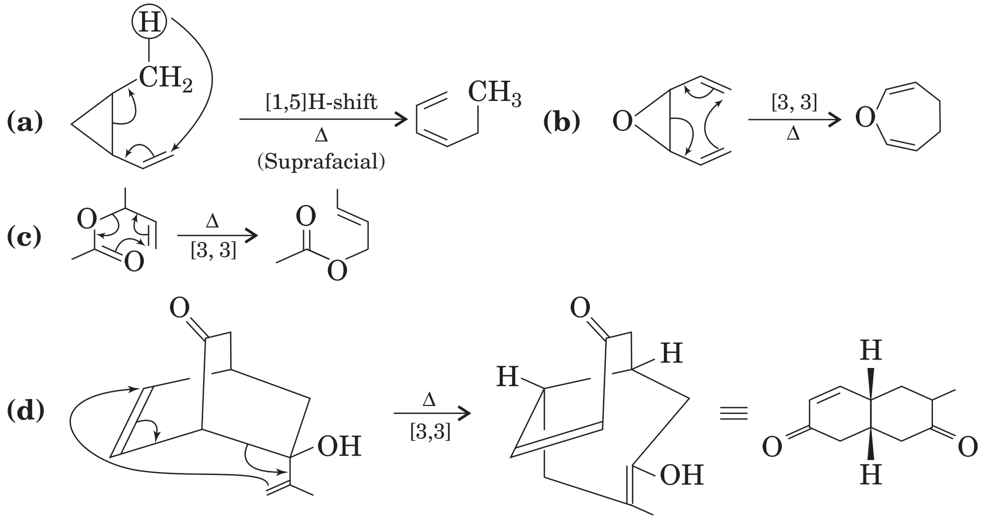
(c)



(d)

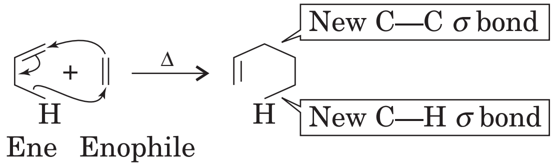


Solution

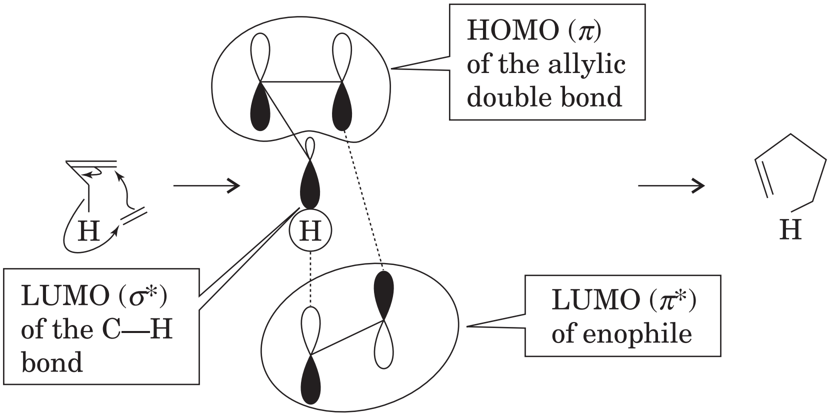


23. What is called an *ene reaction*? Give a suitable example and explain with FMO approach.

Solution An olefin containing an allylic hydrogen atom (the ene) reacts thermally with a multiple covalent bond like C═C, C═O, N═N etc. (the enophile) with the formation of a new σ-bond to the terminal carbon of the allyl group and migration of the allylic C—H σ-bond to one end of the enophile simultaneously. This reaction resembling both cycloaddition and a [1,5] sigmatropic shift of hydrogen is known as the ene reaction.



The ene reaction is always a six-electron reaction. The FMO interaction involves the HOMO of the allylic C═C bond, LUMO of the allylic C—H bond and the LUMO of the enophile. The formation of C—H and C—C σ bond take place in suprafacial fashion.


HOMO (π) of the allylic double bond
H
H
H
LUMO (σ*) of the C—H bond
LUMO (π*) of enophile

24. Provide a convenient way (a mnemonic method) for remembering the selection rules without re-deriving them using the phase relationships.

Solution A very easy way to remember the selection rules for predicting the feasibility of a pericyclic reaction is given below:

(i) Thermal and photochemical reactions are to be assigned +1 and –1, respectively. (ii) The reactions involving (4*n* + 2) and 4*n* electrons are to assigned +1 and –1, respectively. (iii) Disrotatory, suprafacial, or retention of configuration is to be assigned +1 and controtatory, antarafacial, or inversion of configuration is to be assigned –1. The stereochemical assignment is to be made for each component of the reaction. Thus, for a sigmatropic reaction or a cycloaddition, two such assignments are to be made. (iv) The resulting numbers are to be multiplied together.

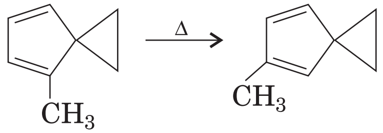
Then, if the product is +1, the reaction is allowed and if it is –1, the reaction is forbidden.

That the thermal [1,3] suprafacial migration of carbon with inversion of configuration in the migrating group is a symmetry-allowed process can be predicted by this method. Now, +1 is to be assigned for the thermal mode, +1 for suprafacial stereo-chemistry on one component, –1 for inversion stereochemistry on the other, and –1 for 4*n* electrons. Then, the result is: (+1) (+1) (–1) (–1) = +1, i.e., the reaction is allowed.

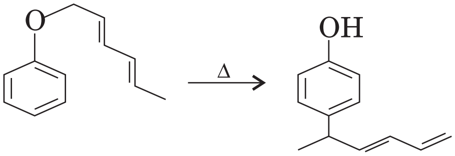
STUDY PROBLEMS

1. Suggest a mechanism for each of the following transformations:

(a)



(b)



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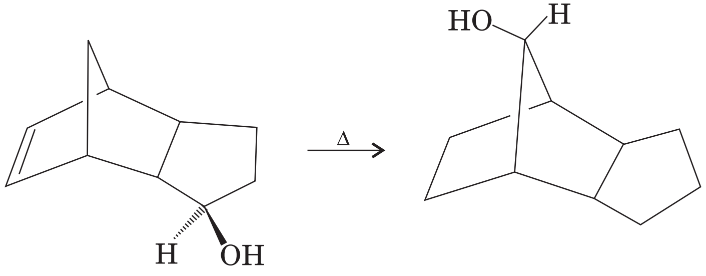
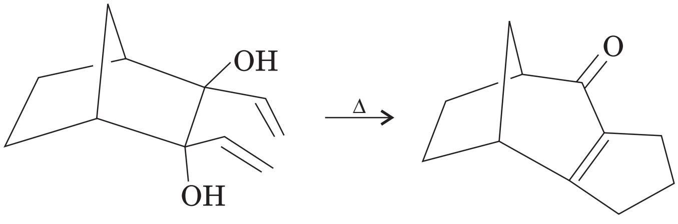
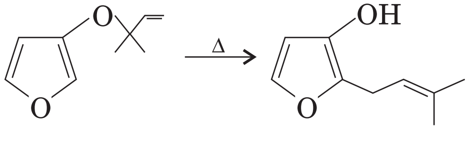
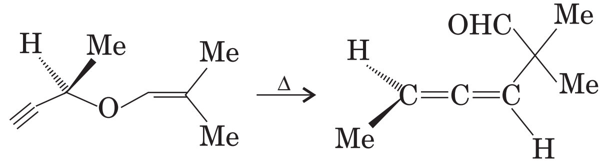


(d)

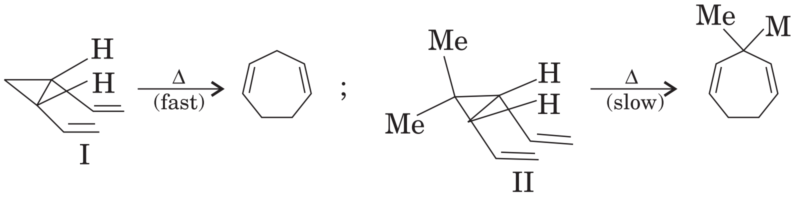


(e)



(f) 

2. *Cis*-1,2-divinyl cyclopropane (I) undergoes Cope rearrangement at a rate faster than the corresponding dimethyl compound (II). Why?

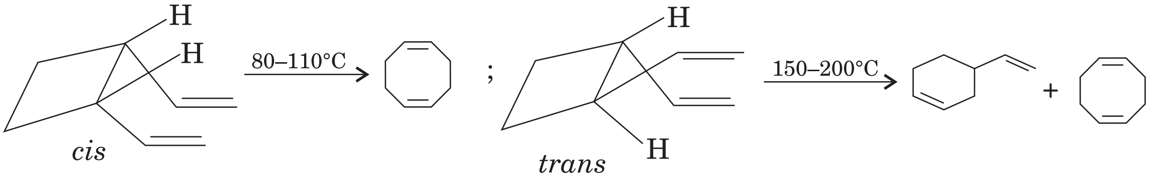


I

II

[**Hint:** Because of steric reason the coiled form of II is much less stable.]

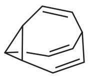
3. Explain why *cis*-1,2-divinylcyclobutane rearranges at a much lower temperature compared to its *trans*-isomer.



cis

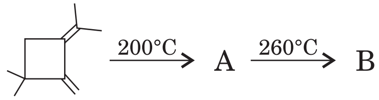
trans

4. The novel hydrocarbon bullvalene ($C_{10}H_{10}$) can undergo rapid [3,3] sigmatropic rearrangements at room temperature. Write an equation illustrating this type of rearrangements in this hydrocarbon.



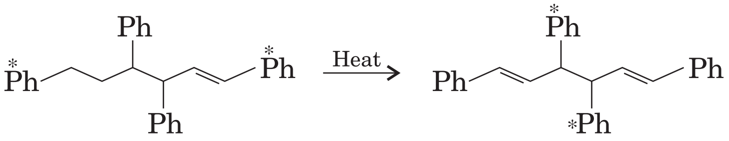
Bullvalene

5. Identify A and B in the following transformation:



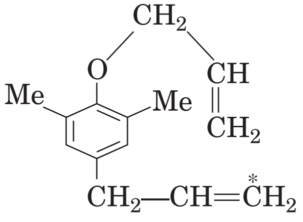
[**Hint:** A [1,5] H-shift followed by electrocyclic ring opening.]

6. Suggest a suitable mechanism for the following reaction:



7. The tautomerism of an enol to a carbonyl compound appears to be a [1,3] sigmatropic H-shift at first glance, but the reaction is catalyzed by base or acid and never proceeds by a concerted pericyclic mechanism. Account for these observations.

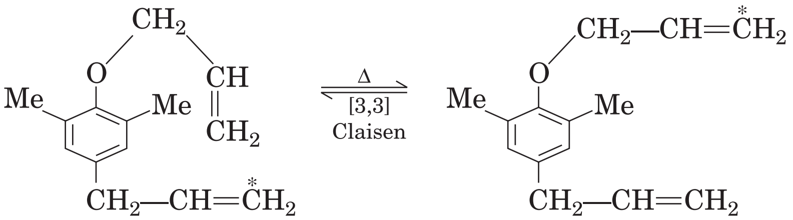
8. What happens when the compound A is heated at 160°C. Explain.



$[\overset{*}{C} = {}^{14}C]$

A

[**Hint:** Heating of the compound A results in the distribution of ^{14}C between its original position and the terminal position of *O*-allyl group. Reversibility of the cyclic mechanism operating in the Claisen rearrangement has been established by this experiment.

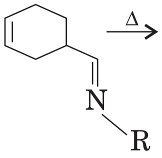


9. (a) Draw the aromatic transition state structure for a [1,5] sigmatropic H-shift.

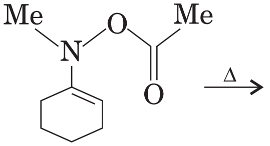
(b) The transition states of the Diels–Alder reaction and the Cope rearrangement are comparable—Why?

10. Write the structure of the product and suggest a mechanism for each of the following variants of the Cope rearrangement:

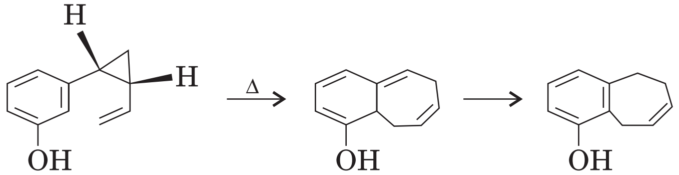
(a)



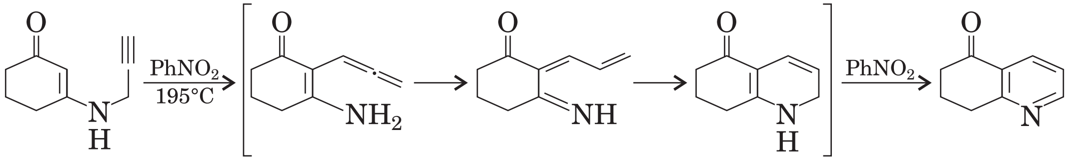
(b)



11. Explain the following observations. When the phenol is heated, a rapid equilibrium is established with a bicyclic compound that does not spontaneously give the final aromatic product unless treated with dilute acid.

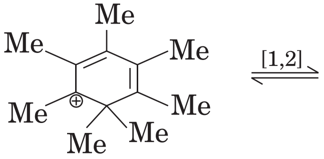


12. Refluxing the following enamine in nitrobenzene gives a pyridine after a series of reactions. Give mechanisms for the reactions and suitable explanations for each pericyclic step.

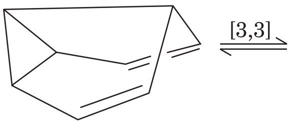


13. Each of the following compounds exists as a fluxional molecule which can undergo interconversion into one or more identical forms by the sigmatropic process indicated. Draw one structure in each case that demonstrates the process of rearrangement involved, and explain why each process is an allowed sigmatropic process.

(a)



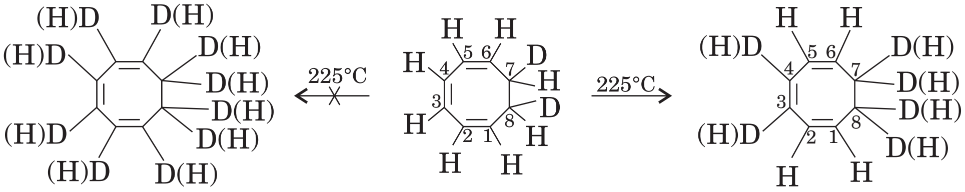
(b)



14. Show by an orbital symmetry analysis that a [3, 3] sigmatropic reaction which is antarafacial with respect to both the components is allowed. Would you think that such a reaction is very common? Give your reasoning.

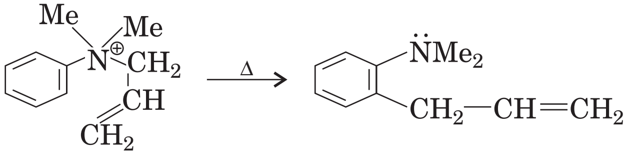
15. Show how the transition state for a [3, 3] sigmatropic reaction can be analyzed as the interaction of two allylic radicals, and that the same stereochemical result is predicted.

16. Explain the following observations:

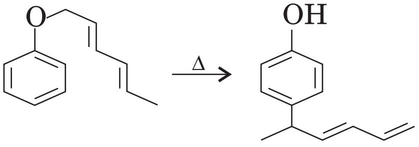


17. Suggest a mechanism for each of the following reactions:

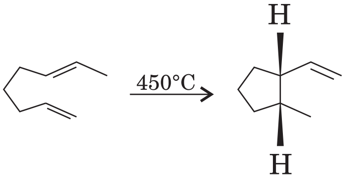
(a)



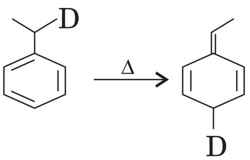
(b)



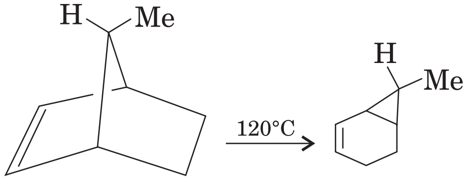
(c)



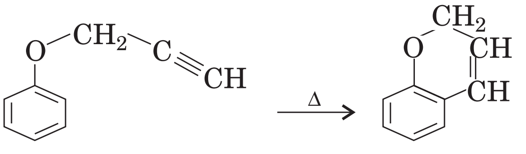
(d)



(e)

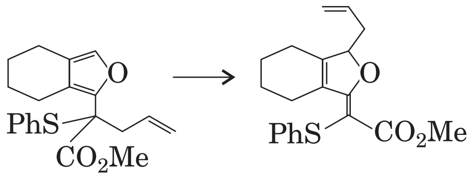


(f)



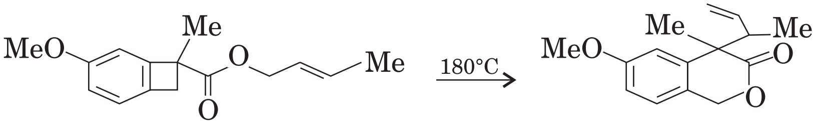
[**Hint:** (f) A [3,3] sigmatropic shift followed by a [1,5] H-shift and electrocyclic ring closure.]

18. The following furan derivative rearranges on standing at room temperature to the product shown. Write two different mechanisms for this transformation.



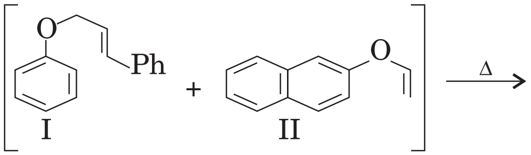
[**Hint:** Mechanism I: a [3,5] sigmatropic rearrangement; Mechanism II: two consecutive [3,3] sigmatropic rearrangements.]

19. Provide a mechanic rationalization for the following transformation and mention the reactions involved:

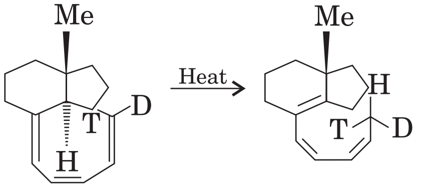


[**Hint:** A 4-electron electrocyclic ring opening followed by a 6π-electrocyclic ring closure and finally [3, 3] sigmatropic rearrangement.]

20. Write all the possible four products when the ethers I and II are heated together. Indicate which of the two products indeed are formed provided the reaction is considered intramolecular.

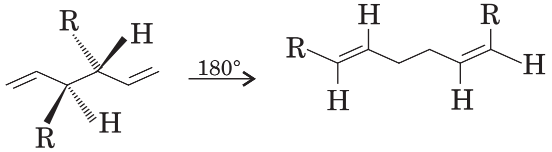


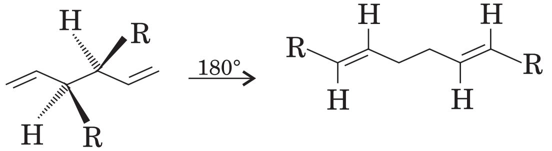
21. Indicate the type of shift takes place in the following transformation and discuss the stereochemical course involved:



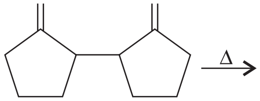
22. Explain the formation of products in the following sigmatropic rearrangements:

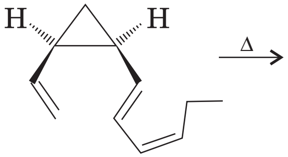
(a)

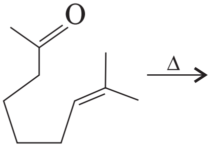


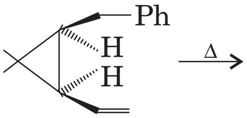
(b) 

23. Give the products expected to be formed in the following reactions:

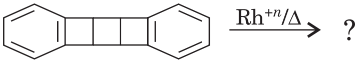
(a) 

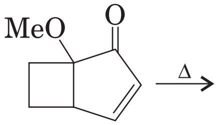
(b) 

(c) 

(d) 

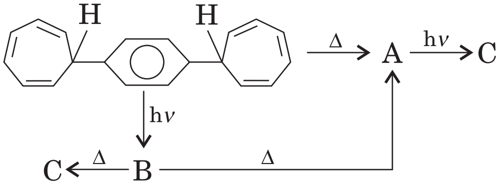
24. Complete the following:

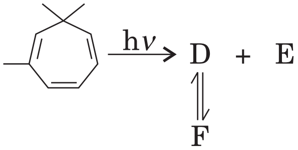
(a) 

(b) 

25. Offer an experiment to show that the Cope rearrangement proceeds through the chair-like transition state rather than boat like transition state and give your reasoning.

26. Identify the compounds A—F in the following reaction sequences:

(a) 

(b) 

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Carbohydrates

9

Chapter Outline

Introduction

9.1 Nomenclature and Classification of Carbohydrates

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- 9.2.1 D and L Designations of Monosaccharides
- 9.2.2 Configurations of Aldoses
- 9.2.3 Configurations of Ketoses
- 9.2.4 Deoxy Sugars
- 9.2.5 Cyclic Structures of Monosaccharides
- 9.2.6 Reactions of Monosaccharides
- 9.2.7 Lengthening the Carbon Chain of Aldoses
- 9.2.8 Shortening the Carbon Chain of Aldoses
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- 9.2.10 Conversion of an Aldose into Its Epimer
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9.4 Polysaccharides
- 9.4.1 Starch
- 9.4.2 Cellulose

INTRODUCTION

Carbohydrates are naturally occurring compounds with the general formula $C_x(H_2O)_y$, where x and y may be same or different. They are called carbohydrates (hydrates of carbon) because they contained hydrogen and oxygen in the same proportion as in water (most of its carbon atoms formally have a molecule of water in the form of an H and an OH). However, a number of compounds have been discovered which are carbohydrates by chemical behaviour but do not conform to the general formula $C_x(H_2O)_y$, for example, 2-deoxyribose which has the molecular formula $C_5H_{10}O_4$. It is also to be noted that all compounds conforming to the formula $C_x(H_2O)_y$ are not necessarily carbohydrates, e.g., formaldehyde, (CH_2O), acetic acid ($C_2H_4O_2$), etc. A few of the carbohydrates are known to everybody, e.g., D-glucose, sucrose (cane sugar), starch, cellulose, etc.

Nearly all carbohydrates, such as sucrose (normal table sugar), taste sweet and are critical to our preparation and enjoyment of the foods that we eat. Carbohydrates are the ultimate source of most of our food we eat. We eat starch-containing grain. We clothe ourselves with cellulose in the form of cotton. We build houses and furniture from cellulose in the form of wood. Thus, carbohydrates quite literally provide us with the major necessities of life.

The simple compounds like CO_2 and water combine to form the sugar D-(+)-glucose. This process, known as photosynthesis, requires catalysis by chlorophyll, and requires energy in the form of light. Thousands of (+)-glucose molecules then combine to form the large molecules of cellulose, which, in fact, constitutes the supporting framework of the plant. (+)-Glucose molecules also combine, in a somewhat different way, to form the large molecules of starch which is then stored in the seeds. When eaten by an animal, the starch is broken down into the original (+)-glucose units. (+)-Glucose is then carried by the blood stream to the tissues, where it is oxidized, ultimately to carbon dioxide and water, with the release of energy. Thus, carbohydrates serve as stores of chemical energy in our bodies.

$$\underset{\text{Glucose}}{C_6H_{12}O_6} + 6O_2 \underset{\text{Photosynthesis}}{\overset{\text{Oxidation}}{\rightleftharpoons}} 6CO_2 + 6H_2O$$

Analysis has revealed that structurally carbohydrates are polyhydroxy aldehydes, polyhydroxy ketones, or compounds that can be hydrolyzed to them. All carbohydrates are optically active.

9.1 NOMENCLATURE AND CLASSIFICATION OF CARBOHYDRATES

The names of simpler carbohydrates end in *–ose*. Carbohydrates with an aldehydic structure are known as *aldoses*, and those with ketonic structure are known as *ketoses*. The number of carbon atoms in the molecule is indicated by a Greek prefix. For example, a *tetrose* contains four carbon atoms, a *pentose* five, a *hexose* six, etc. If the nature of the carbonyl group in the molecule is known then that is also included in the name. For example, glucose, a six-carbon polyhydroxy aldehyde, is an aldohexose, whereas fructose, a six-carbon polyhydroxy ketone, is a ketohexose.

Carbohydrates are divided into two major classes and these are (i) **sugars** and (ii) **polysaccharides**. Sugars are crystalline substances with a sweet taste and soluble in water. Polysaccharides, on the other hand, are more complex than sugars, their molecular masses being far greater. Most of the polysaccharides are noncrystalline solids, which are not sweet, and are insoluble or less soluble in water compared to sugars. The terms *carbohydrate*, *saccharide* and *sugar* are used interchangeably. *Saccharide* comes from the word for sugar in various early languages (*sakcharon* in Greek, *Sarkara* in Sanskrit, and *saccharum* in Latin).

Sugars are divided into two main classes: (i) **Monosaccharides** and (ii) **Oligosaccharides.**

(i) Monosaccharides (monosaccharoses) These are sugars, i.e., polyhydroxy aldehydes or ketones, which cannot be hydrolysed into still smaller molecules of carbohydrate. The general formula of monosaccharides is $C_nH_{2n}O_2$ (there are exceptions), where n is 2 to 10. Pentoses and hexoses are, in fact, the most important monosaccharides. Examples include glucose, fructose, mannose, etc.

(ii) Oligosaccharides These are carbohydrate molecules which yield 2–10 molecules of monosaccharides on hydrolysis. The carbohydrates that undergo hydrolysis to yield two monosaccharide molecules (same or different) are called *disaccharides*. Examples are sucrose, maltose, galactose, cellobiose, etc.

$$\underset{\text{Sucrose}}{C_{12}H_{22}O_{11}} + H_2O \longrightarrow \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Fructose}}{C_6H_{12}O_6}$$

Disaccharides

Monosaccharides

$$\underset{\text{Galactose}}{C_{12}H_{22}O_{11}} + H_2O \longrightarrow \underset{\text{Glucose}}{2\,C_6H_{12}O_6}$$

Similarly, a *trisaccharide* yields three molecules of monosaccharides on hydrolysis. Raffinose, for example, is a trisaccharide which on hydrolysis produces galactose, glucose, and fructose.

Sugars are further classified under the heads: (i) *Reducing sugars* and (ii) *Non-reducing sugars*.

(i) Reducing sugars are those which reduce ammoniacal silver nitrate solution, Fehling solution, etc. *All monosaccharides are reducing sugars*. D-glucose and D-fructose are, therefore, reducing sugars. An oligosaccharide, on the other hand, may or may not be a reducing sugar. (+)-Mannose and (+)-lactose are reducing dissacharides.

(ii) Non-reducing sugars are those which cannot reduce ammoniacal silver nitrate solution, Fehling solution, etc. Cane sugar (sucrose), for example, is a non-reducing sugar.

Polysaccharides (polysaccharoses) These are carbohydrates which yield a large number of monosaccharide molecules on hydrolysis. The most widely spread polysaccharides are starch, cellulose, etc. Both starch and cellulose are glucose polymers. A group of polysaccharides which are less widely spread in nature is the *pentosans*, $(C_5H_8O_4)_n$. Polysaccharides are amorphous, water-insoluble substances which are not sweet to taste.

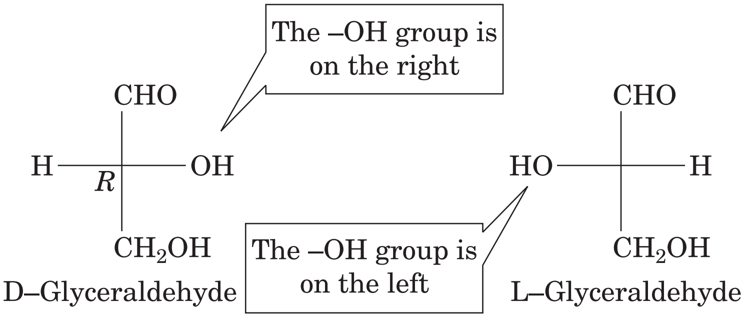
$$\underset{\substack{\text{Starch}\\ \text{or cellulose}\\ \text{(a polysaccharide)}}}{(C_6H_{10}O_5)_n} + nH_2O \xrightarrow[\text{hydrol.}]{\text{HCl}} \underset{\substack{\text{Glucose}\\ \text{(a monosaccharide)}}}{nC_6H_{12}O_6}$$

9.2 MONOSACCHARIDES

9.2.1 D and L Designations of Monosaccharides

Although the *R*, *S* system can be used to describe the configuration of one or more of the asymmetric carbon atoms of a monosaccharide, a different system, however, was in use long before the *R*, *S* system was established. The D, L system (first proposed by M.A. Rasanoff of New York University in 1906) is used for this purpose. As this system is applied to carbohydrates, the configuration of a carbohydrate enantiomer is specified by applying the conventions given below:

1. The *R* enantiomer (the –OH group is on the right) of the naturally occurring aldotriose glyceraldehyde is arbitrarily said to have the D configuration, whereas its enantiomer (in which the –OH group is on the left) is said to have the L configuration.

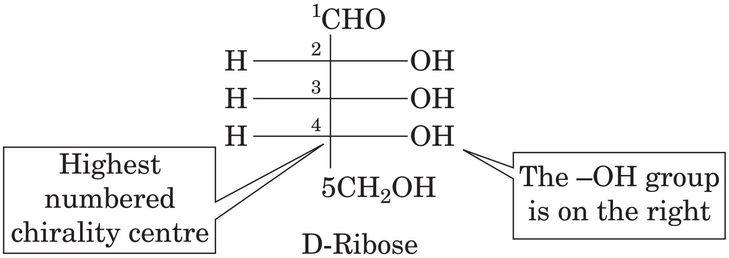


These two compounds serve as configurational standards for all monosaccharides.

2. The other aldoses or ketoses are written in a Fischer projection with their carbonyl group placed always on top (in the case of aldoses or as close to the top as possible (in the case of ketoses). The carbons in the straight vertical line are then numbered consecutively as they would be in systematic nomenclature, so that the carbonyl carbon receives the lower possible number.
3. The chiral carbon of highest number is designated as a reference carbon. If this carbon has H, OH and CH_2OH groups in the same relative configuration as the same three groups of D-glyceraldehyde, the carbohydrate molecule is said to have the D configuration. If this carbon has the same configuration as L-glyceraldehyde, the carbohydrate molecule is said to have the L configuration. That is, if the –OH group attached to the bottommost asymmetric centre (the carbon second from the bottom) is on the right, then the compound is a D-sugar and if the same –OH group is on the left, the compound is an L-sugar. Almost all sugars found in nature are D-sugars. The mirror image of a D-sugar is an L-sugar.

The applications of these conventions is illustrated by the following examples:

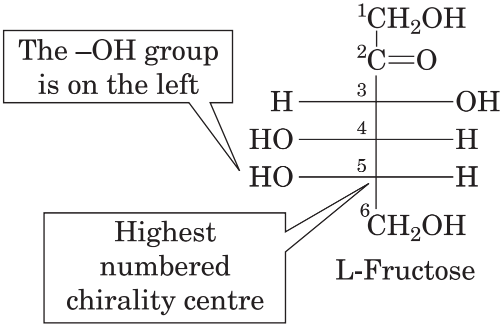
(i)


1CHO
2
3
4
H
H
H
OH
OH
OH
5CH2OH
Highest numbered chirality centre
The –OH group is on the right

D-Ribose

This aldopentose is known as D-ribose. D- in that sense, the highest numbered asymmetric carbon atom (i.e., C-4) has the –OH group on the right as in D-glyceraldehyde.

(ii)

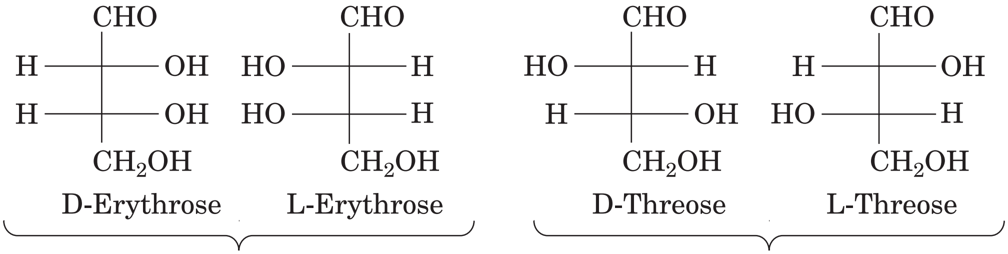

1CH2OH
2C=O
3
4
5
6CH2OH
H
HO
HO
OH
H
H
The –OH group is on the left
Highest numbered chirality centre

L-Fructose

This ketohexose is known as L-fructose. L- in that sense, the highest numbered asymmetric carbon atom (i.e., C-5) has the –OH group on the left as in L-glyceraldehyde.

9.2.2 Configurations of Aldoses

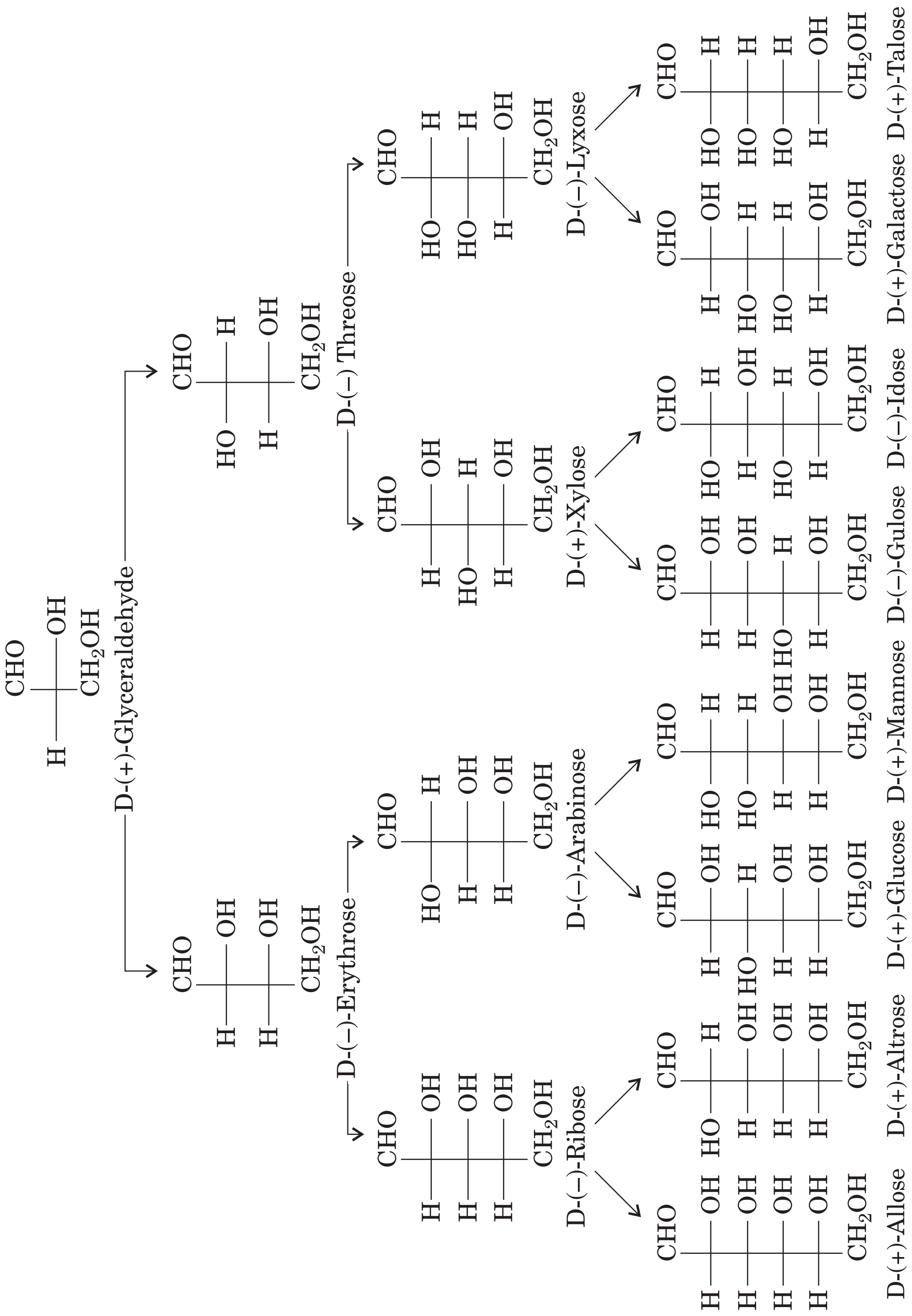
Aldotetroses have two chirality centres and therefore four stereoisomers. Two of them are D-sugars and two of them are L-sugars. The names of the aldotetroses—erythrose and threose - were used to name the erythro and threo pairs of enantiomers.



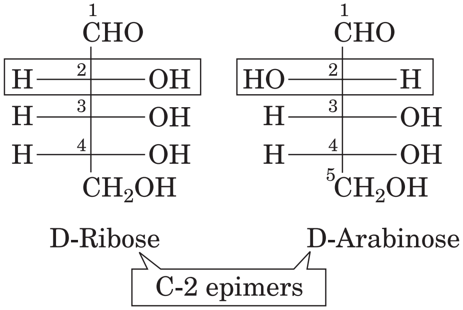
D-Erythrose L-Erythrose D-Threose L-Threose

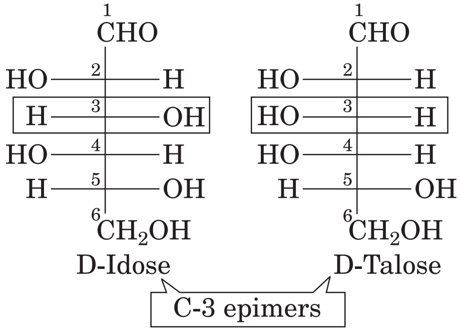
enantiomers enantiomers

Aldopentoses having three asymmetric centres exist as eight stereoisomers (four pairs of enantiomers). Aldohexoses having 4 asymmetric centres exist as 16 stereoisomers (8 pairs of enantiomers). The family tree of the D series of aldoses containing three through six carbon atoms may be drawn as follows:


D-(+)-Glyceraldehyde
D-(−)-Erythrose
D-(−) Threose
D-(−)-Ribose
D-(−)-Arabinose
D-(+)-Xylose
D-(−)-Lyxose
D-(+)-Allose
D-(+)-Altrose
D-(+)-Glucose
D-(+)-Mannose
D-(−)-Gulose
D-(−)-Idose
D-(+)-Galactose
D-(+)-Talose

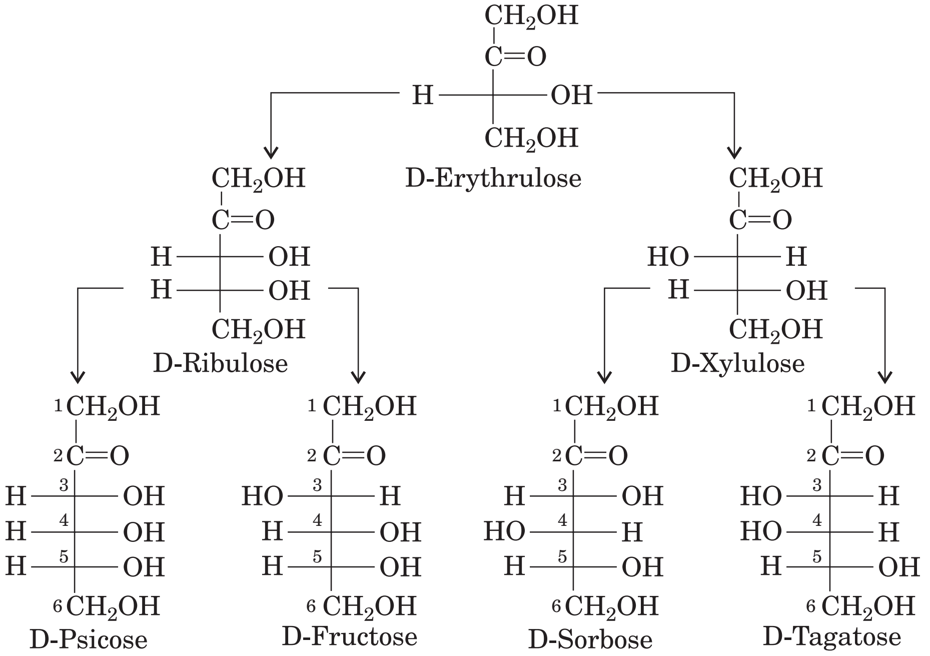
Epimers Diastereoisomers that differ in configuration at only one chirality centre are called epimers. For example, D-ribose and D-arabinose are C-2 epimers because they differ in configuration only at C-2. Similarly, D-idose and D-talose are C-3 epimers.





9.2.3 Configuration of Ketoses

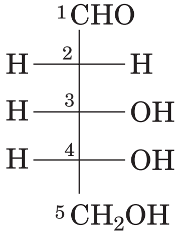
A ketose has one less chirality centre than an aldose with the same number of carbon atoms and because of this, a ketose has only half as many stereoisomers as an aldose with the same number of carbons. The family tree of the D series of ketoses containing four through six carbon atoms may be drawn as follows:



D-Psicose and D-fructose are C-3 epimers, whereas D-psicose and D-sorbose are C-4 epimers.

9.2.4 Deoxy Sugars

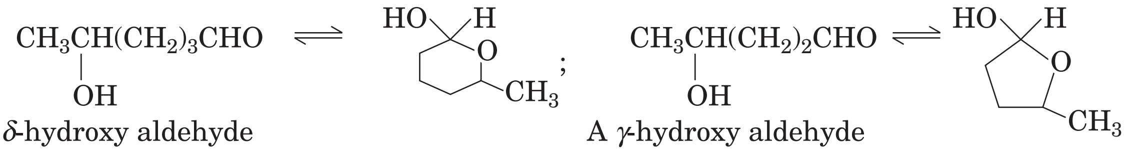
Some naturally occurring sugars have a hydrogen atom in place of one or more of the –OH groups. These are called deoxy sugars. For example:



2-Deoxy-D-ribose

9.2.5 Cyclic Structures of Monosaccharides

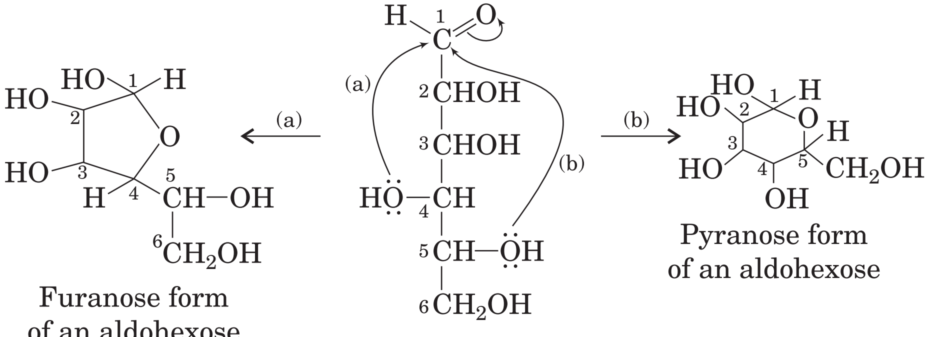
As a result of intramolecular nucleophilic addition of an alcohol function to a carbonyl group, *γ*- or *δ*-hydroxy aldehydes exist predominantly as cyclic hemiacetals. Such intramolecular reactions are thermodynamically more favoured than the corresponding intermolecular reactions because the entropy contribution to the free energy is less unfavourable in the former reactions compared to the latter reactions.



A *δ*-hydroxy aldehyde

A *γ*-hydroxy aldehyde

The same is true of aldoses and ketoses. Although monosaccharides are frequently written as acyclic carbonyl compounds, they exist predominantly as cyclic hemiacetals. For example, in aqueous solution, (+)-glucose exist almost exclusively (99.99%) as its cyclic hemiacetal form along with a very small amount of the open-chain form. Many of the monosaccharides exist both as five- and six-membered cyclic hemiacetals. These can be obtained when the –OH group on C-4 or on C-5 becomes involved in cyclization. A six-membered cyclic hemiacetal is called a **pyranose**, derived from the name of the six-membered cyclic ether **pyran**. A five-membered cyclic hemiacetal is called a **furanose**, derived from the name of the five-membered cyclic ether **furan**.



Furanose form
of an aldohexose

Open-chain form
of an aldohexose

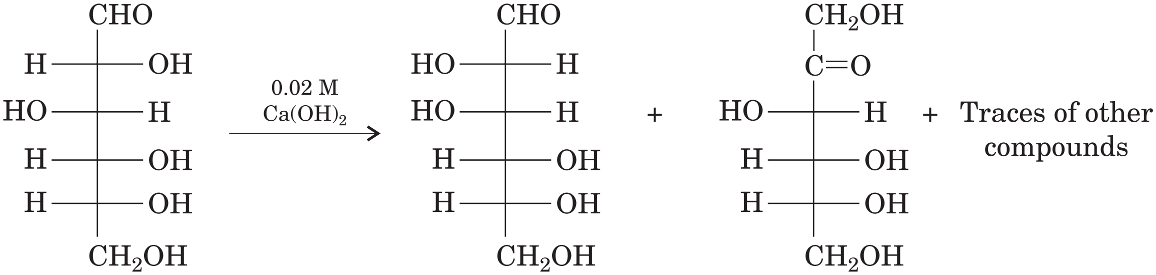
Pyranose form
of an aldohexose

Pyranose forms are usually present in greater amounts than furanose forms at equilibrium and this is because six-membered rings are less strained compared to the five-membered rings.

9.2.6 Reactions of Monosaccharides

9.2.6.1 Reactions of Monosaccharides in Basic Solutions

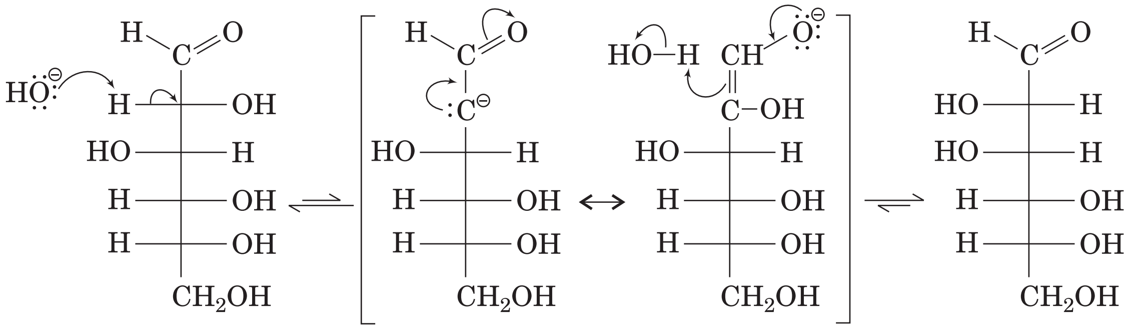
When monosaccharides are dissolved in aqueous base, they undergo a series of enolizations and keto-enol tautomerization that lead to isomerizations. For example, if a solution of D-glucose containing calcium hydroxide (0.02 M) is allowed to stand for a long time, a number of products can be isolated including D-mannose and D-fructose. This type of reaction is called the **Lobry de Bruyn–Alberda–van Ekenstein reaction**, named after the two Dutch chemists who discovered it in 1895.



D-Glucose D-Mannose D-Fructose

D-Mannose is obtained by **base-catalyzed epimerization** and D-fructose is obtained by an **enediol rearrangement**.

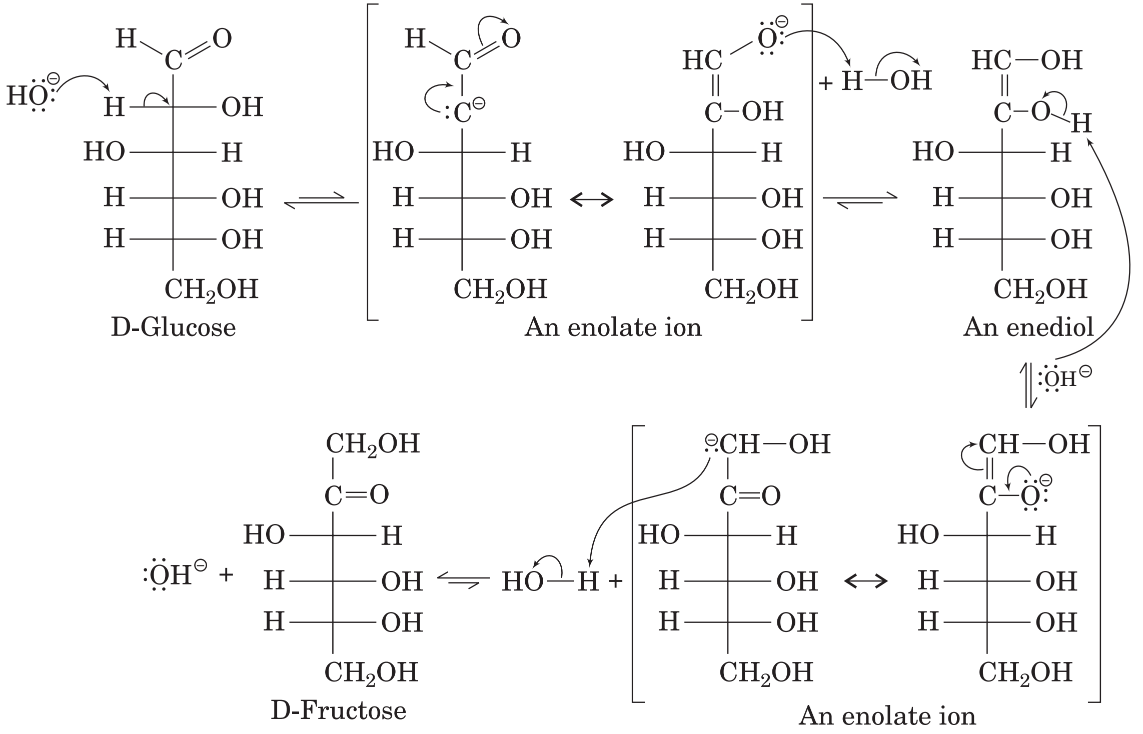
Mechanism for the base-catalyzed epimerization and formation of D-mannose:



D-Glucose An enolate ion D-Mannose

Although D-glucose in solution exists mainly in its cyclic hemiacetal forms, it also remains in equilibrium with a small amount of its acyclic aldehyde form. This aldehyde containing an α-hydrogen ionizes to give small amounts of its enolate ion in base. Protonation of the enolate ion at one face of the double bond gives back D-glucose, whereas protonation at the other face gives D-mannose (the C-2 epimer). Because the reaction forms a pair of epimers, it is called epimerization.

Mechanism for the base catalyzed enediol rearrangement and formation of D-fructose:



The base removes a proton from the α-carbon to form an enolate ion. The enolate ion then undergoes protonation to form an **enediol**. The enediol containing a hydroxy group at each end of a double bond is simultaneously the enol of not only the aldoses D-glucose and D-mannose, but also the ketose D-fructose. Tautomerization of the –OH group, at C-1 reproduces D-glucose or produces D-mannose, whereas tautomerization of the –OH group at C-2 produces D-fructose.

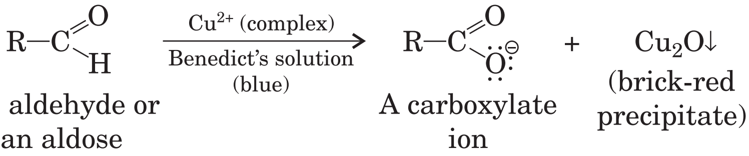
When base abstracts a proton from C-3 of D-fructose, a different enediol is formed which may tautomerize to give a ketose with the carbonyl group at C-2 or C-3. Thus, the carbonyl group can be moved up and down the carbon chain.

When reactions with monosaccharides are carried out, it is usually important to prevent these base-catalyzed isomerizations and thereby to preserve the stereochemistry at all of the chiral centres. This can be done by converting a monosaccharide to the corresponding methyl glycoside first. The reactions in basic medium can then safely carried out because the —CHO group has been converted to an acetal and acetals are stable in aqueous base. Hence, a monosaccharide can be protected from undesired reactions by preparing its methyl glycoside.

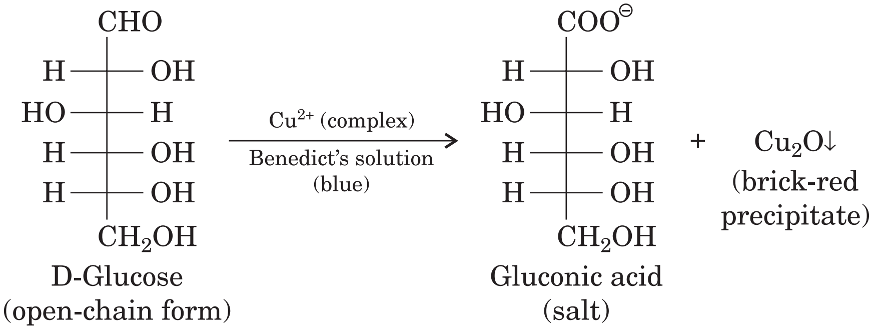
9.2.6.2 Oxidation Reactions of Monosaccharides

A number of oxidizing agents are used for identification of functional groups of carbohydrates, in their structure elucidations, and for their syntheses and these are (1) Benedict's or Tollens' reagents, (2) bromine water, (3) nitric acid, and (4) periodic acid.

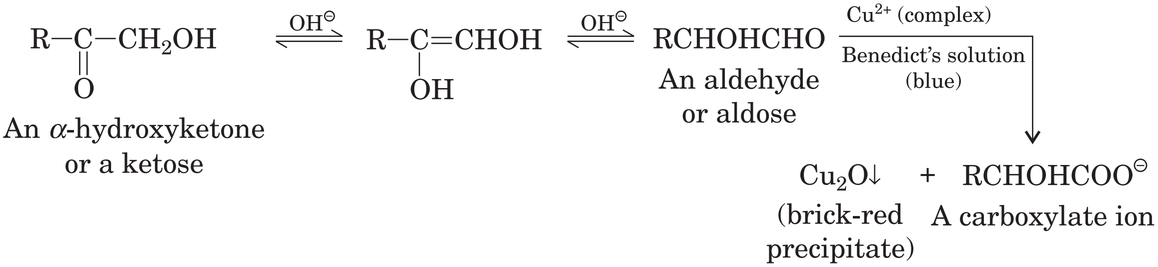
(1) Benedict's or Tollens' reagents Benedict's reagent (an alkaline solution containing a cupric citrate complex ion) oxidizes aldehydes to the corresponding carboxylic acid (salt). The formation of a brick-red precipitate of cuprous oxide (Cu_2O) by reduction of Cu(II) is taken as a positive test for aldehydes. Aldoses, therefore, give positive tests with this reagent, even though they exist primarily as cyclic hemiacetals.



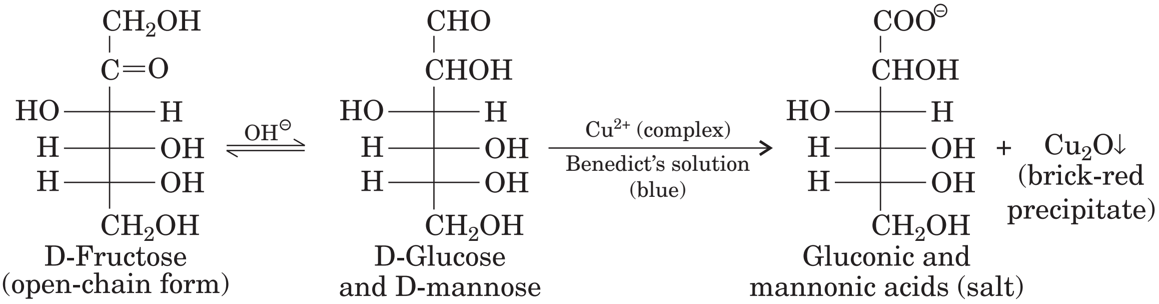
Glucose, for example, reacts as follows:



α-Hydroxyketones also give a positive test with Benedict's solution and this is because in alkaline solution they are converted to aldehydes through the formation of enediol intermediates, and the aldehydes then reduce Benedict's solution. Ketoses, therefore, give positive tests with this reagent, even though they exist primarily as cyclic hemiacetals.

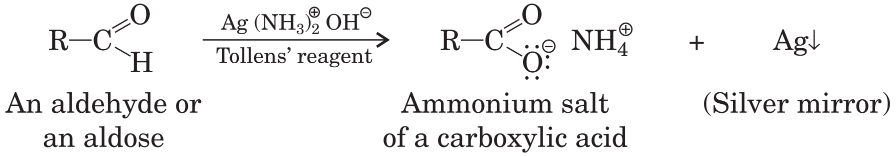


Fructose, for example, reacts as follows:

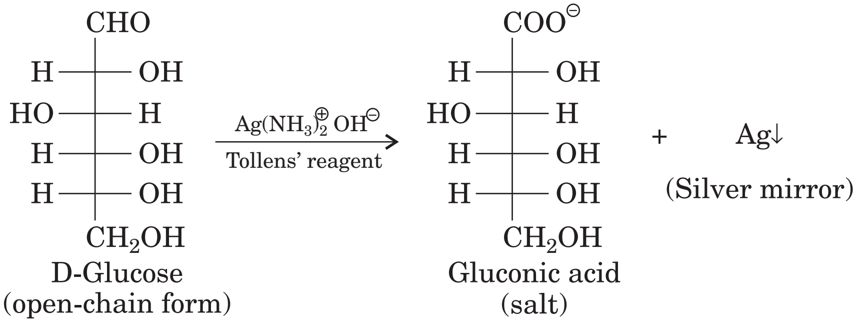


(Fehling's solution, a similar alkaline reagent containing a cupric ion-complexed with tartrate ion, can also be used as a test for aldoses and ketoses.)

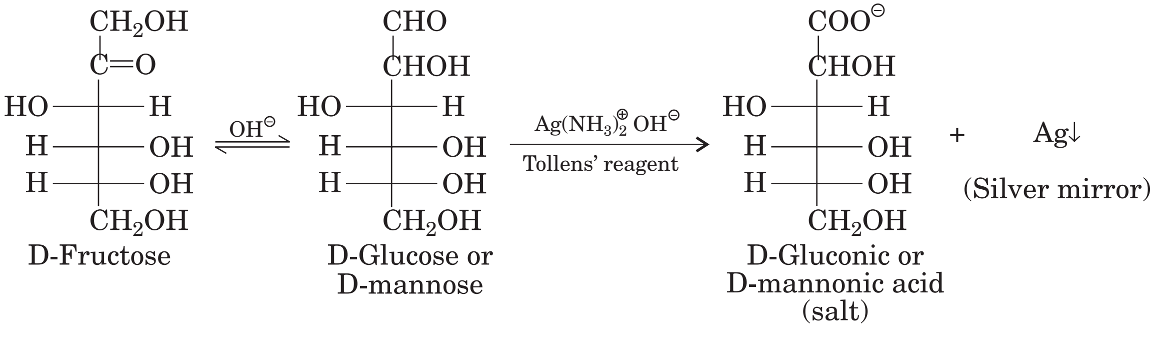
Aldehydes reduce Tollens' reagent and thereby they are oxidized to give carboxylate ions and metallic silver, often in the form of a silver mirror on the inside of the test tube. Thus, aldehydes and aldoses give positive test with this reagent.



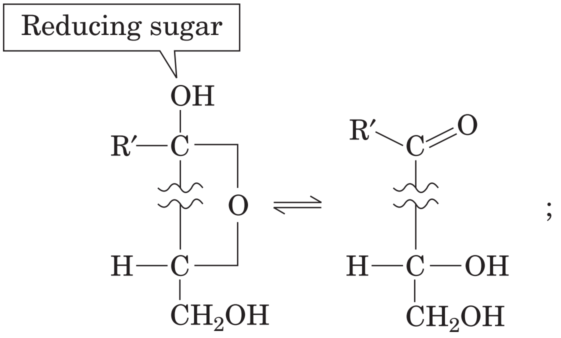
Glucose, for example, reacts as follows:



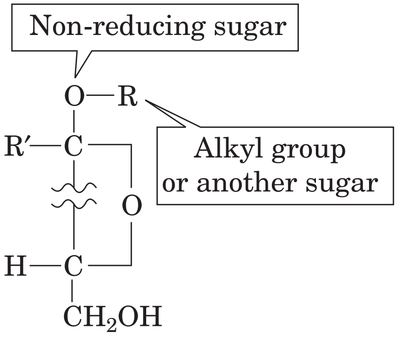
Due to isomerization in the alkaline medium (discussed earlier), ketoses also respond to this test. For example:



Since both aldoses and ketoses give positive tests with Benedict's and Tollens' reagents, neither of them can be used to distinguish between aldoses and ketoses, i.e., we cannot distinguish D-glucose and D-fructose using these reagents. Again, both of these reagents cannot be used as a preparative reagent in carbohydrate oxidations. This is due to the fact that oxidation with these reagents takes place in alkaline solution, and in alkaline medium, sugars undergo a series of reactions leading to isomerizations and fragmentations.

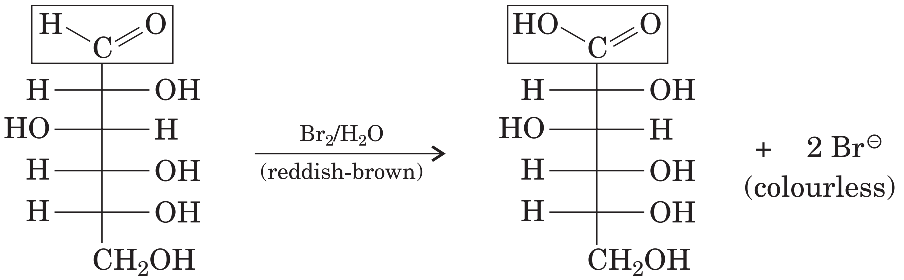


Hemiacetal (R′═H or CH_2OH) of an aldose or a ketose (gives positive Benedict's or Tollens' test)



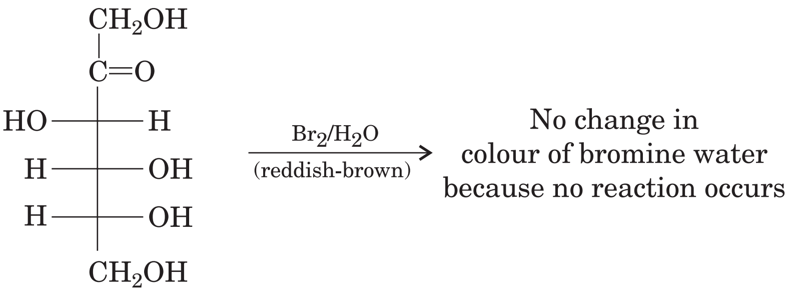
Acetal (R′═H or CH_2OH) of an aldose or a ketose (does not give a positive Tollens' or Benedict's test because it cannot equilibrate with the corresponding aldehyde or α-hydroxyketone)

(2) Bromine water Aldoses can be distinguished from ketoses by observing what happens to the reddish-brown colour of an aqueous solution of Br_2 when it is added to the sugar. Being a mild oxidizing agent, Br_2 easily oxidizes the aldehyde group, but it cannot oxidize ketoses and alcohols. Therefore, when a small amount of an aqueous solution of Br_2 is added to an unknown monosaccharide, the reddish-brown colour of Br_2 disappears, because Br_2 will be reduced to colourless $Br^{\ominus}$) if the monosaccharide is an aldose but persists if the monosaccharide is a ketose. Bromine water is also a useful oxidizing reagent for preparative purposes because it selectively oxidizes the —CHO group to a —COOH group, thus converting an aldose to an *aldonic acid*. Also, because the solution is mildly acidic (pH 6.0), monosaccharides do not undergo isomerization and fragmentation reactions in bromide water. For example:



D-Glucose (an aldose)

D-Gluconic acid (an aldonic acid)

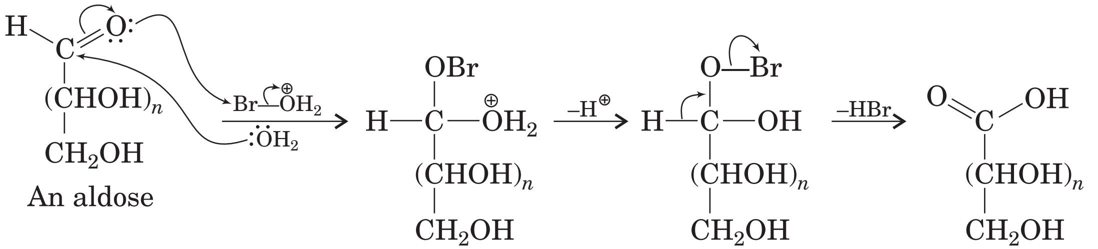


No change in colour of bromine water because no reaction occurs

D-Fructose (a ketose)

Mechanism for oxidation:

$$Br_2 + H_2O \rightarrow HOBr + HBr \rightleftharpoons H_2\overset{\oplus}{O}\text{—}Br + Br^{\ominus}$$



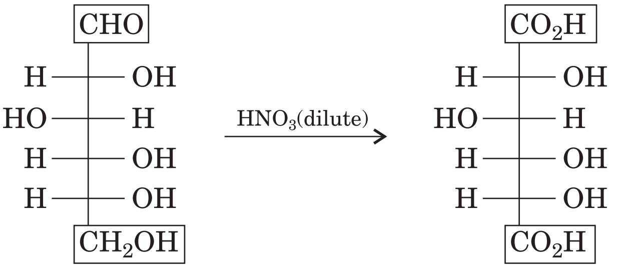
An aldose

An aldonic acid

(3) Nitric acid Dilute nitric acid is a stronger oxidizing agent than bromine water, Tollens' or Benedict's reagents or Fehling's solution, oxidizing both the aldehyde (—CHO) and the primary alcohol group (—CH_2OH) of an aldose to —COOH group (without affecting secondary alcohol groups). Consequently, this is a very useful reagent for converting aldoses into dicarboxylic acids known as *aldaric acids*.

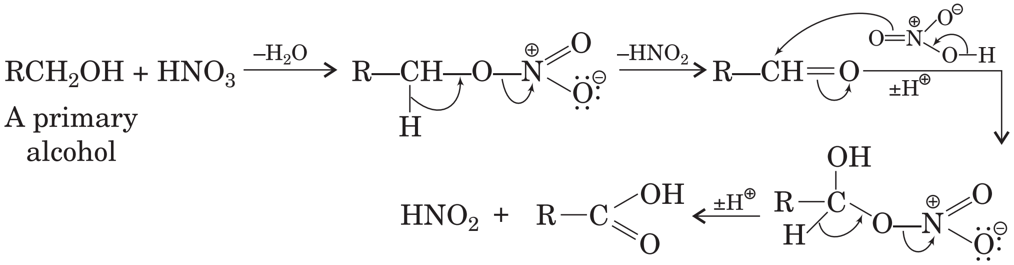
$$\underset{\text{An aldose}}{HOCH_2(CHOH)nCHO} \xrightarrow{HNO_3\text{ (dilute)}} \underset{\text{An aldaric acid}}{HO_2C(CHOH)_nCO_2H}$$

D-Glucose, for example, produces D-Glucaric acid:



D-Glucose D-Glucaric acid

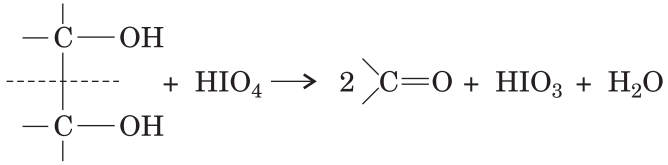
Mechanism for HNO_3 oxidation:



A primary alcohol

A carboxylic acid

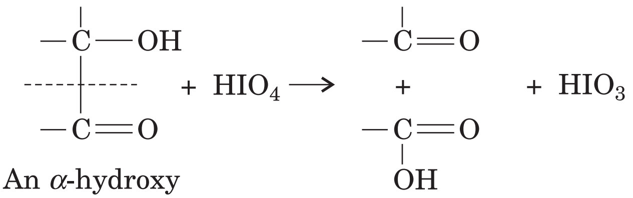
(4) Periodic acid (HIO_4) Compounds containing hydroxyl groups on adjacent carbon atoms (1,2-diols) undergo oxidative cleavage when they are allowed to react with periodic acid. The reaction causes C—C bond cleavage and yields carbonyl compounds (aldehydes, ketones, or acids). Each C—C bond cleavage requires one mole of HIO_4 and for every C—C bond broken, a C—O bond is formed at each carbon. $NaIO_4$ can also be used instead of HIO_4.



$$\begin{array}{c} -\overset{|}{C}-OH \\ -\underset{|}{C}-OH \end{array} + HIO_4 \longrightarrow 2\,\rangle C{=}O + HIO_3 + H_2O$$

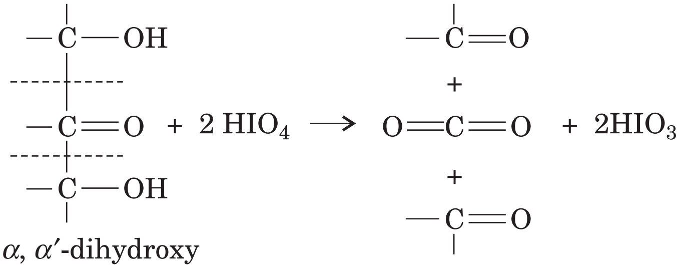
A 1,2-diol

α-Hydroxy aldehydes or ketones and α,α'-dihydroxy ketones also undergo oxidative cleavage by periodic acid. An α-hydroxy carbonyl compound yields one molar equivalent of a carboxylic acid and one molar equivalent of an aldehyde or a ketone, whereas an α,α'-dihydroxy ketone yields two molar equivalents of carbonyl compound and one molar equivalent of carbon dioxide.



$$\begin{array}{c} -\overset{|}{C}-OH \\ -C{=}O \end{array} + HIO_4 \longrightarrow \begin{array}{c} -\overset{|}{C}{=}O \\ + \\ -\underset{\displaystyle OH}{\underset{|}{C}}{=}O \end{array} + HIO_3$$

An α-hydroxy aldehyde or ketone

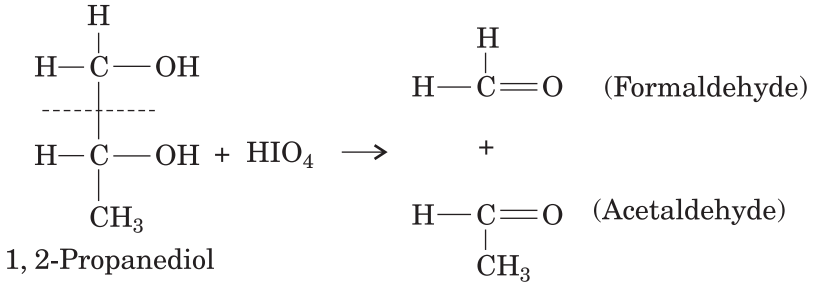


$$\begin{array}{c} -\overset{|}{C}-OH \\ -C{=}O \\ -\underset{|}{C}-OH \end{array} + 2\,HIO_4 \longrightarrow \begin{array}{c} -\overset{|}{C}{=}O \\ + \\ O{=}C{=}O \\ + \\ -\underset{|}{C}{=}O \end{array} + 2HIO_3$$

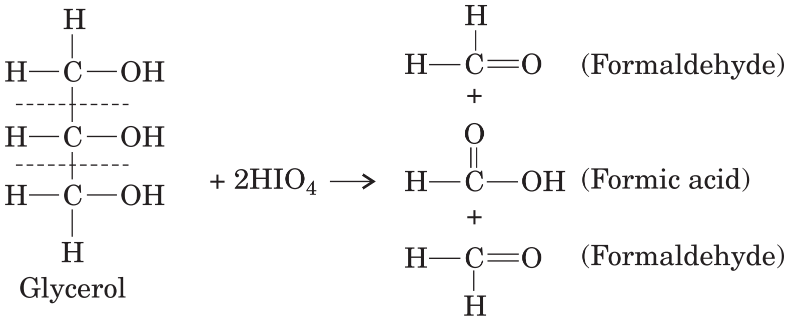
An α, α'-dihydroxy ketone

It is to be noted that α-hydroxy acids or esters do not undergo oxidative cleavage. The course of the reaction may be well illustrated with some simple examples.

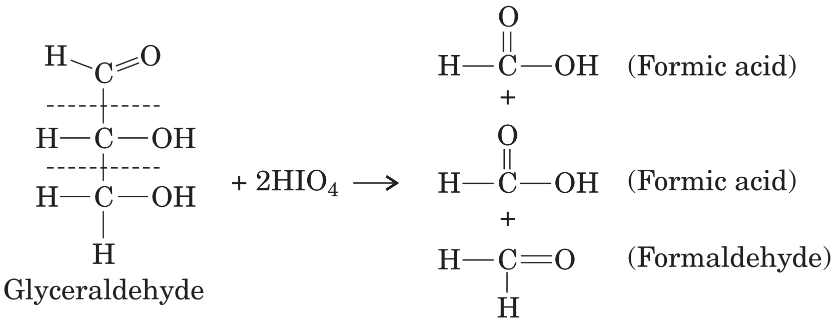
(i) Oxidation of 1,2-propanediol When 1,2-propanediol is subjected to periodic acid oxidation, one molar equivalent of formaldehyde and one molar equivalent of acetaldehyde are obtained.



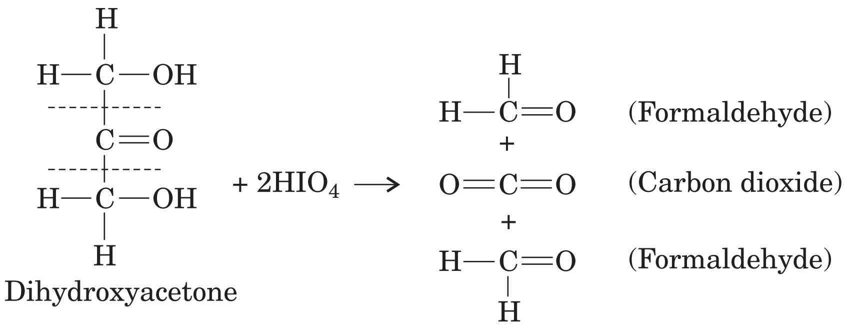
(ii) Oxidation of glycerol When three or more —CHOH— groups are contiguous, the internal ones are converted to formic acid. Periodic acid oxidation of glycerol gives two molar equivalents of formaldehyde and one molar equivalent of formic acid.



(iii) Oxidation of glyceraldehyde When subjected to react with HIO_4, glyceraldehyde yields one molar equivalent of formaldehyde and two molar equivalents of formic acid.



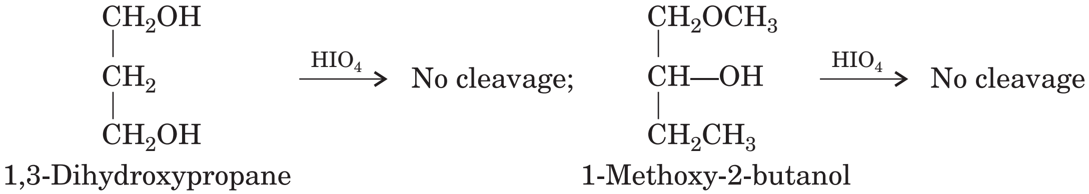
(iv) Oxidation of dihydroxyacetone When dihydroxyacetone is oxidized with periodic acid, two molar equivalents of formaldehyde and one molar equivalent of carbon dioxide are obtained.



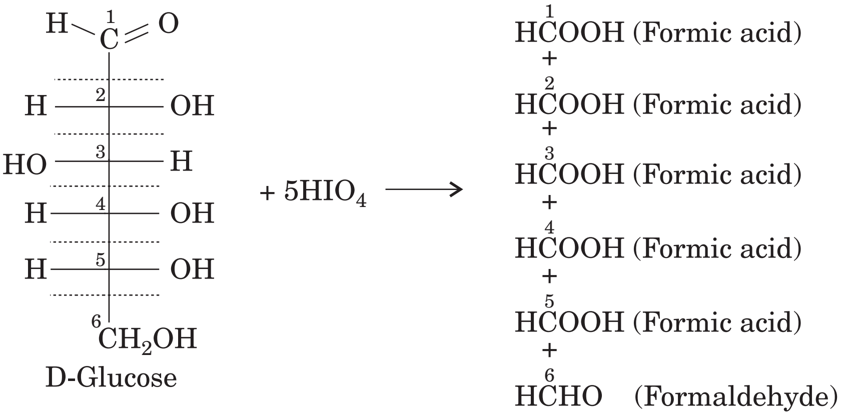
Therefore, in a polyhydroxy aldehyde, a —CHO and an internal —CHOH— group are oxidized to formic acid, and a terminal —CH_2OH group is oxidized to formaldehyde. In a polyhydroxy ketone, a $>$C=O group is oxidized to carbon dioxide. In all these reactions, one mole of periodic acid is used for each pair of adjacent alcoholic groups or an alcoholic group adjacent to a C=O group.

Since these reactions usually takes place in quantitative yield, valuable information about the structure of the molecule can often be obtained by measuring the number of molar equivalents of HIO_4 that are consumed in these reactions as well as by identifying the products and measuring the amount of formic acid and formaldehyde produced.

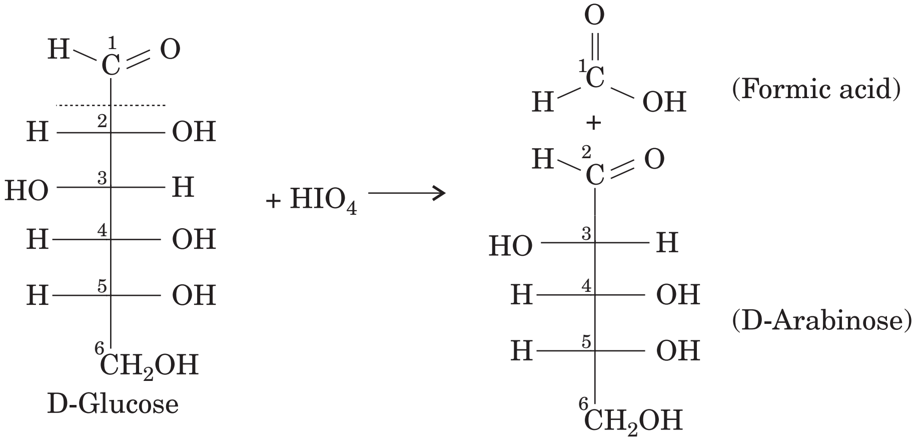
It is to be noted that HIO_4 does not cleave compounds in which the hydroxyl groups are separated by an intervening methylene (—CH_2—) group, nor those in which an –OH group is adjacent to an ether or acetal function. For example:



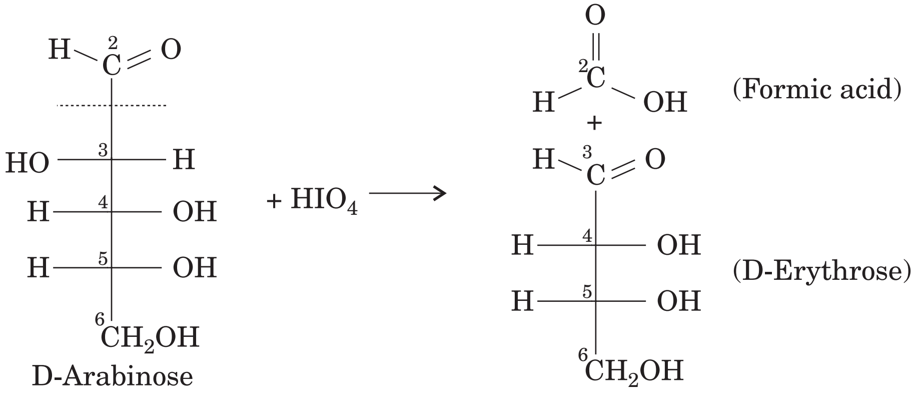
Periodic acid oxidation of D-glucose The oxidation of this aldohexose requires five moles of periodic acid and produces one mole of formaldehyde and five moles of formic acid.



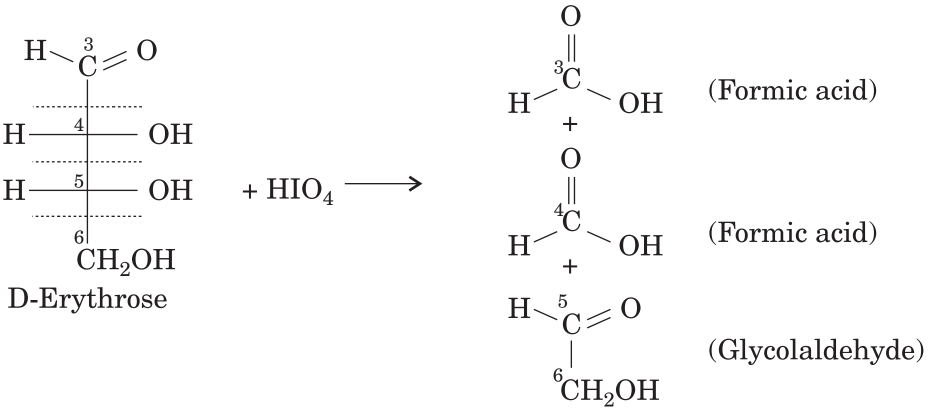
To explain this product mixture one may carry out the oxidation process down the chain. Since the upper end of the molecule is an α-hydroxy aldehyde moiety, it should produce formic acid and an aldehyde (containing one less carbon) upon oxidation.



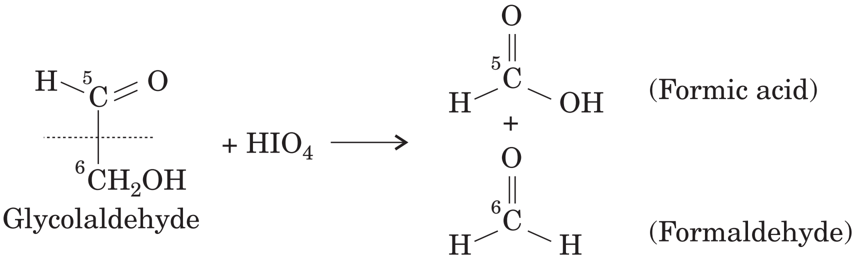
Being an α-hydroxy aldehyde D-arabinose will also undergo oxidative cleavage to form a second molecule of formic acid and D-erythrose (an α-hydroxy aldehyde).



This process continues twice more and as a result, two more formic acid molecules and one molecule of glycolaldehyden are formed.

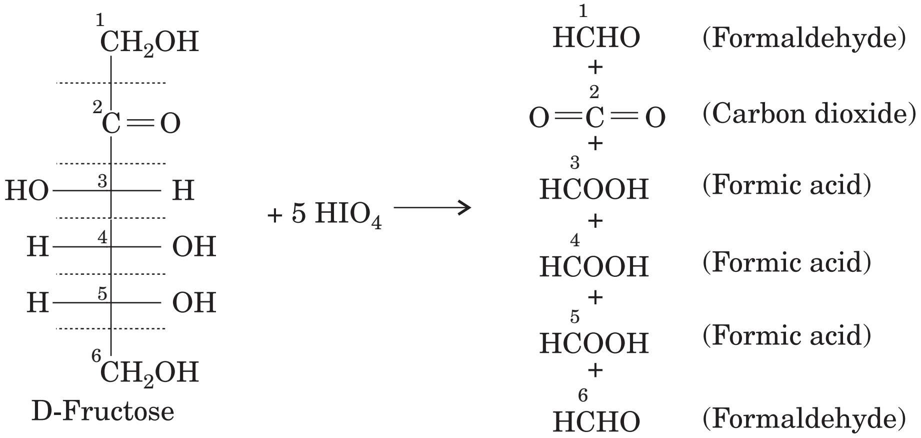


This last α-hydroxy aldehyde also undergoes oxidative cleavage by HIO_4 to yield formic acid and formaldehyde in 1:1 molar ratio.



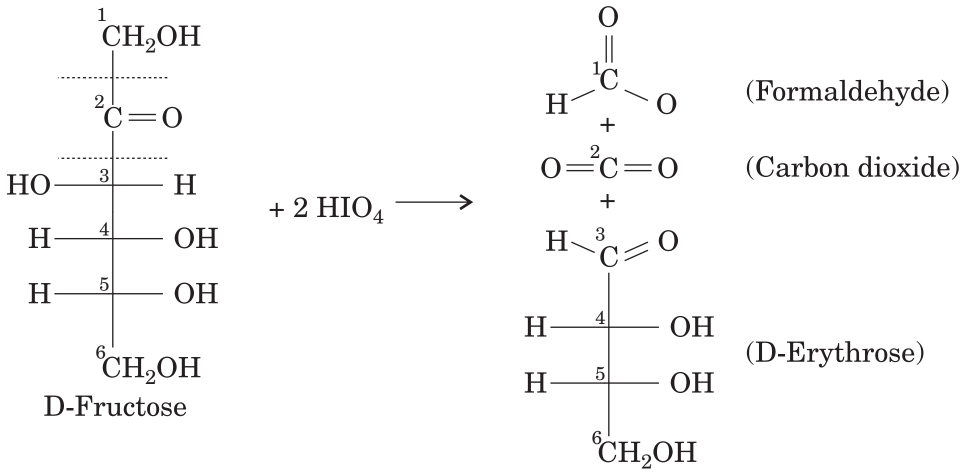
Therefore, when all the above steps are added up, we see that D-glucose on HIO_4 oxidation should yield five molar equivalents of formic acid and one molar equivalent of formaldehyde.

Periodic oxidation of D-fructose The oxidation of this ketohexose requires five moles of periodic acid and produces two moles of formaldehyde, three moles of formic acid and one mole of carbon dioxide.

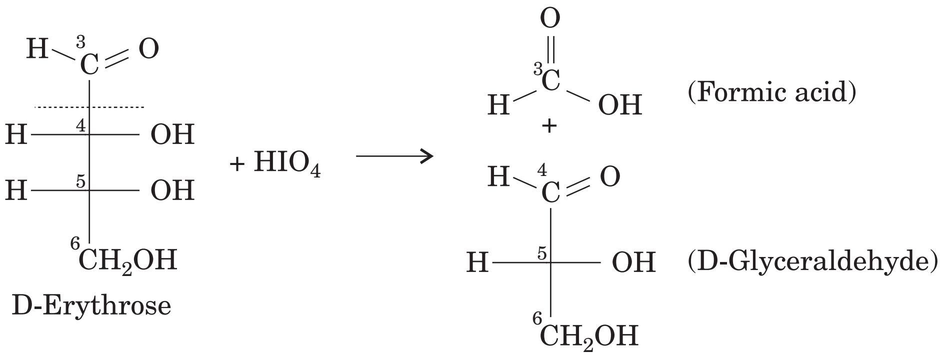


In this case also, we can start the process of oxidative cleavage from the top of the molecule, i.e., from C-1–C-2 bond. Since the upper end of the molecule is an α-hydroxy-ketone moiety, it should yield formaldehyde and a carboxylic acid upon oxidation.

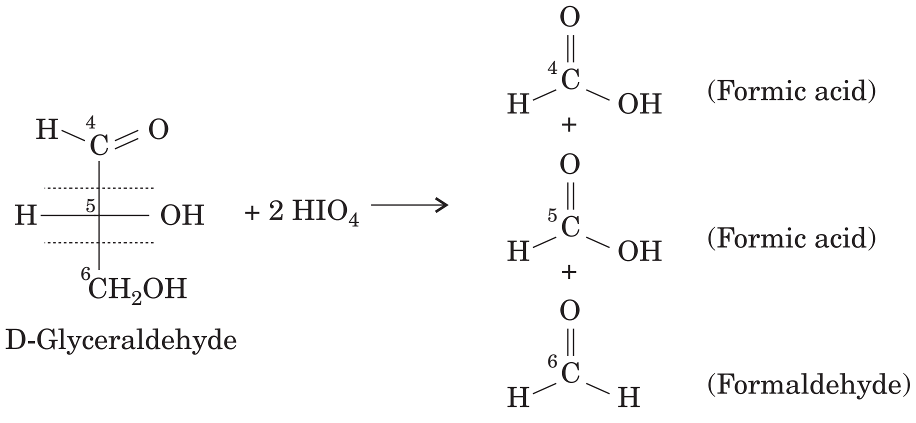
However, the α-hydroxy acid does not undergo oxidative cleavage by HIO_4. Because of this, the α-α'-dihydroxy ketone moiety undergoes oxidative cleavage of two C—C bonds simultaneously by two molar equivalents of HIO_4 to yield formaldehyde, CO_2, and D-erythrose (an α-hydroxy aldehyde).



D-Erythrose then undergoes oxidative cleavage to form formic acid and D-glyceraldehyde (an α-hydroxy aldehyde).



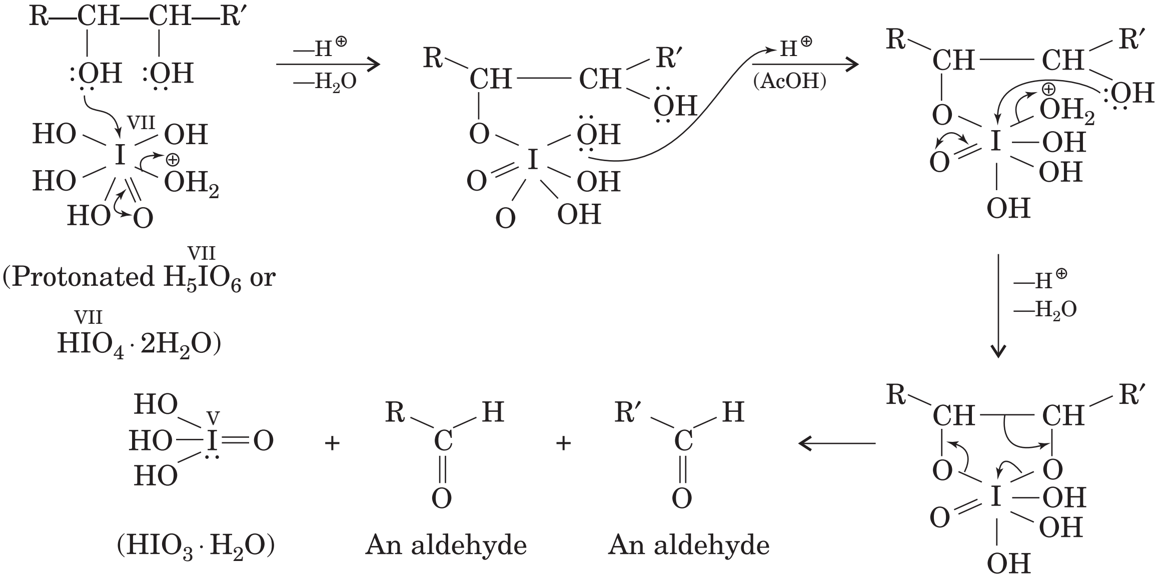
The process is repeated twice to yield two molar equivalents of formic acid and one molar equivalent of formaldehyde through the intermediate formation of glycolaldehyde.



When all these steps are added up, we see that D-fructose is expected to yield two molar equivalents of HCHO, three molar equivalents of HCOOH and one molar equivalent of CO_2.

Mechanism for periodic acid oxidation The oxidation actually involves periodic acid hydrate (H_5IO_6 or $HIO_4 \cdot 2H_2O$) in the presence of aqueous acetic acid (AcOH).

(i) 1,2-Diols:



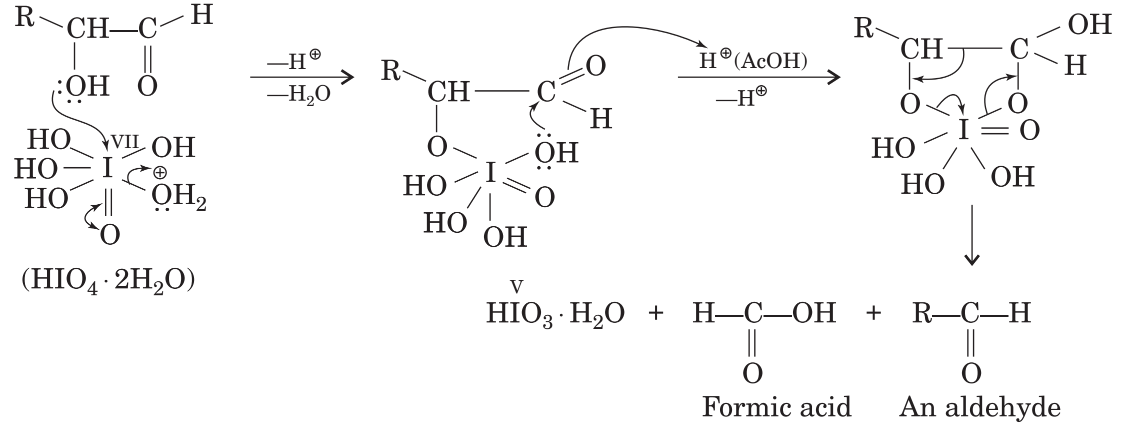
(Protonated $\overset{VII}{H_5IO_6}$ or $\overset{VII}{HIO_4} \cdot 2H_2O$)

($HIO_3 \cdot H_2O$) An aldehyde An aldehyde

The cleavage of glycols with HIO_4 occurs through the formation of a cyclic periodate ester intermediate. The cyclic ester then breaks down by a cyclic flow of electrons in which the central iodine atom accepts an electron pair and is reduced.

[A cyclic intermediate is attainable only with a *cis*-diol and for this reason, a *trans*-diol cannot be cleaved by periodic acid oxidation.]

(ii) α-Hydroxy carbonyl compounds:

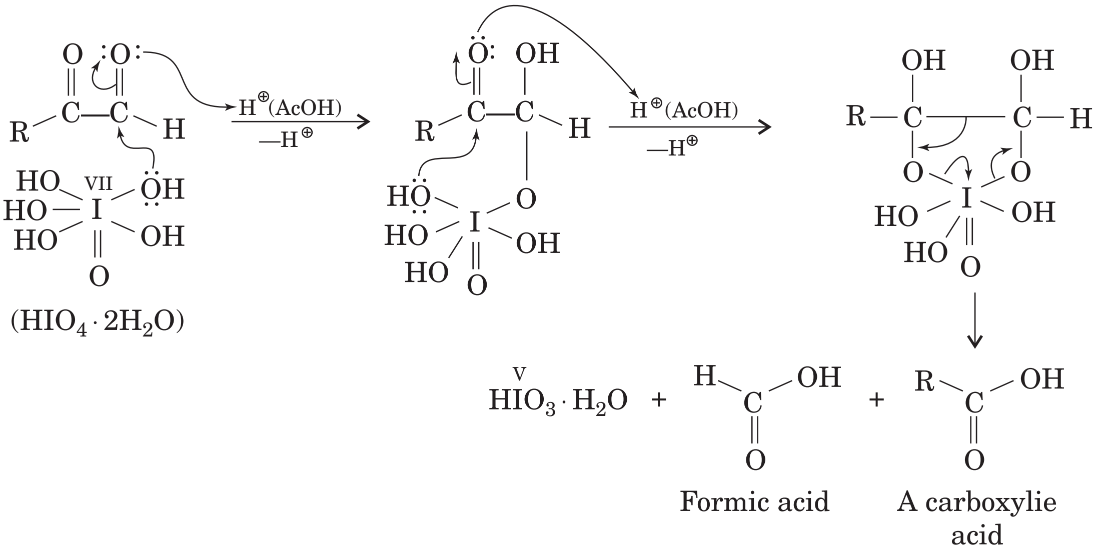


($HIO_4 \cdot 2H_2O$)

$\overset{V}{HIO_3} \cdot H_2O$ + H—C(=O)—OH + R—C(=O)—H

Formic acid An aldehyde

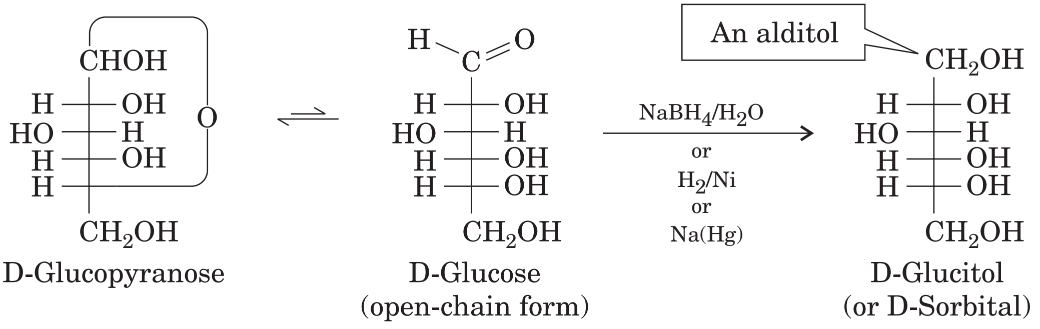
(iii) **1,2-Dicarbonyl compounds:**



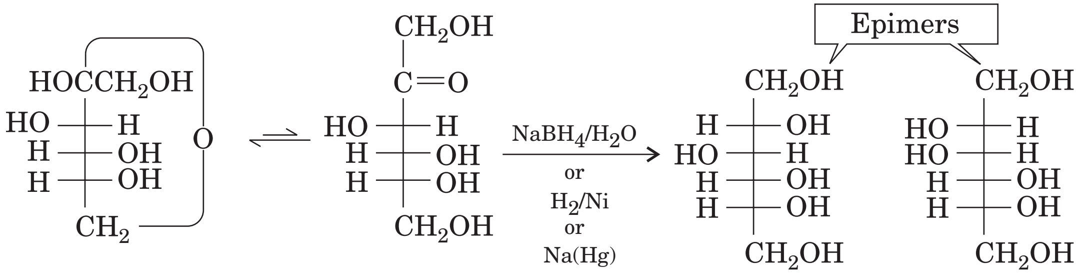
9.2.6.3 *Reduction of Monosaccharides: Alditols*

1. Using $NaBH_4$, H_2/Raney nickel or Na/Hg Like ordinary aldehydes and ketones the carbonyl group in aldoses and ketoses can be reduced by sodium borohydride ($NaBH_4$). The product of the reduction is a polyalcohol, known as *alditol*

Alditols are named by adding the suffix-*itol* to the root name of the sugar. Catalytic hydrogenation (H_2 with a Raney nickel catalyst in aqueous ethanol) and $Na(Hg)/H_2O$ can also be used for the same transformation.



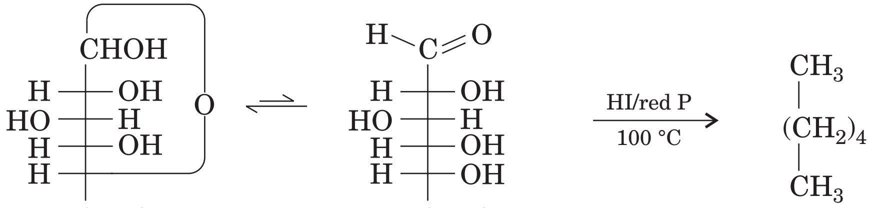
The reduction of a ketose forms two alditols because the reaction creates a new chirality centre in the product. For example, the reduction of D-fructose form D-mannitol and D-glucitol, the C-2 epimer of D-mannitol.



D-Fructopyranose D-Fructose D-Glucitol D-Mannitol

The reduction in the case of aldose as well as ketose occurs on the small amount of the open-chain form that is present in equilibrium with the cyclic form. Once it reacts, it is immediately replenished (Le chatelier's principle). As a result, the equilibrium continuously shifts until all the sugar is reduced.

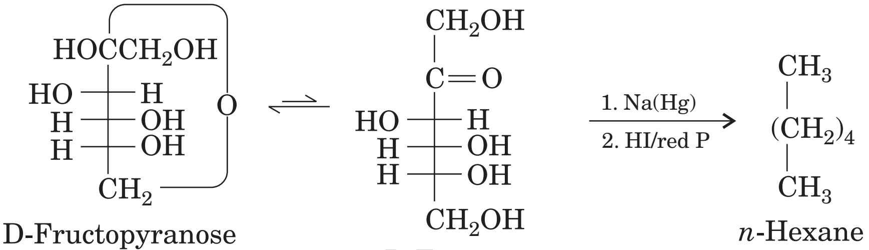
3. Using conc. HI and red phosphorus When an aldose is heated for a long time with concentrated hydroiodic acid and red phosphorus at 100°C, it undergoes reduction to give the corresponding alkane. For example, D-glucose produces *n*-hexane.



D-Glucopyranose D-Glucose (open-chain form) *n*-Hexane

A ketohexose cannot be reduced to the corresponding alkane by heating with conc. HI/red P. However, on successive reduction with Na(Hg) and HI/red P, they form the corresponding alkane.

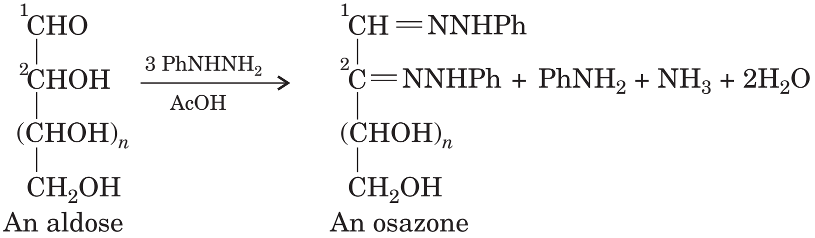
For example, the ketohexone fructose produces *n*-hexane.



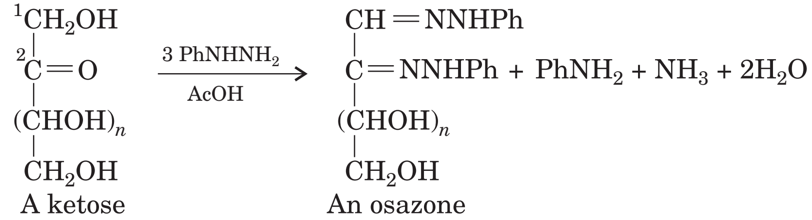
D-Fructopyranose D-Fructose (open-chain form) *n*-Hexane

9.2.6.4 Reactions of Monosaccharides with Three Molar Equivalents of Phenylhydrazine: Formation of Osazone

As aldehydes and ketones, aldoses and ketoses react with phenylhydrazine under acidic conditions to form phenylhydrazones. However, when an excess of phenylhydrazine is used, the reaction proceeds further by consuming two more molar equivalents of phenylhydrazine to yield yellow crystalline solids called *osazones* (here phenylosazone), which contains two phenyl hydrazine residues (at C-1 and C-2) per molecule. Unlike sugars osazones crystallize readily and are useful derivatives for identifying sugars.



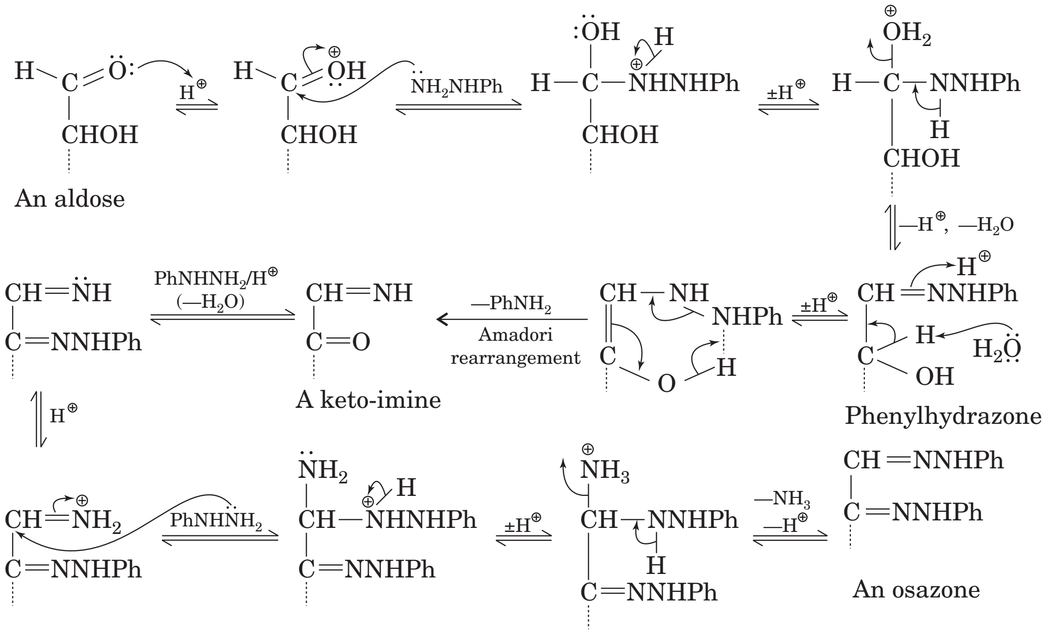
$$\begin{array}{l} {}^{1}CHO \\ | \\ {}^{2}CHOH \\ | \\ (CHOH)_n \\ | \\ CH_2OH \end{array} \xrightarrow[AcOH]{3\ PhNHNH_2} \begin{array}{l} {}^{1}CH=NNHPh \\ | \\ {}^{2}C=NNHPh \\ | \\ (CHOH)_n \\ | \\ CH_2OH \end{array} + PhNH_2 + NH_3 + 2H_2O$$



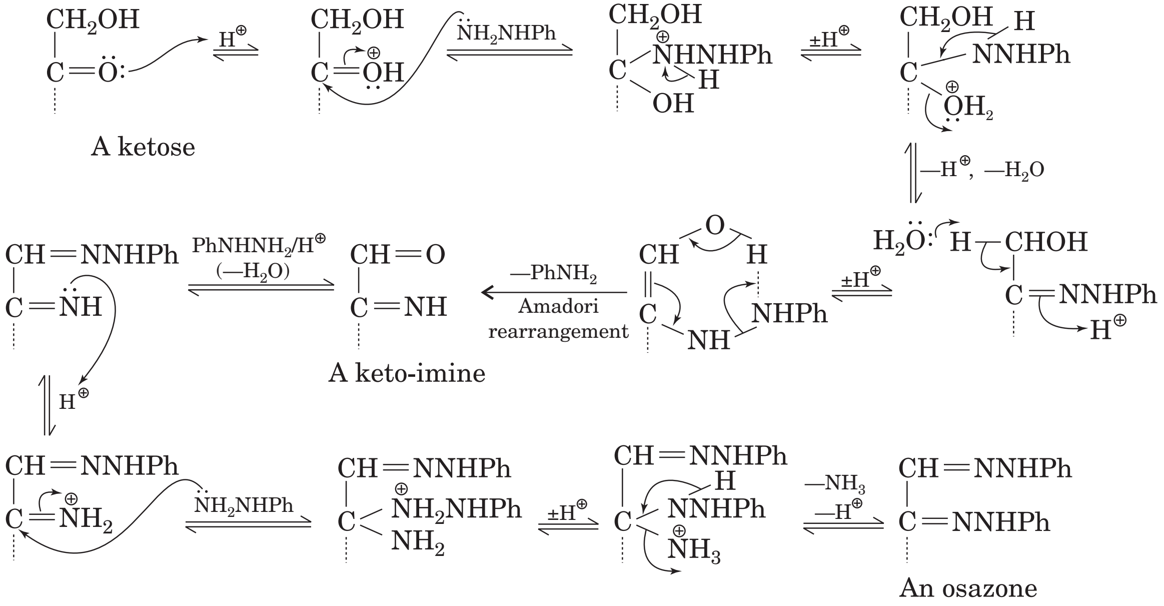
$$\begin{array}{l} {}^{1}CH_2OH \\ | \\ {}^{2}C=O \\ | \\ (CHOH)_n \\ | \\ CH_2OH \end{array} \xrightarrow[AcOH]{3\ PhNHNH_2} \begin{array}{l} CH=NNHPh \\ | \\ C=NNHPh \\ | \\ (CHOH)_n \\ | \\ CH_2OH \end{array} + PhNH_2 + NH_3 + 2H_2O$$

Mechanism for osazone formation

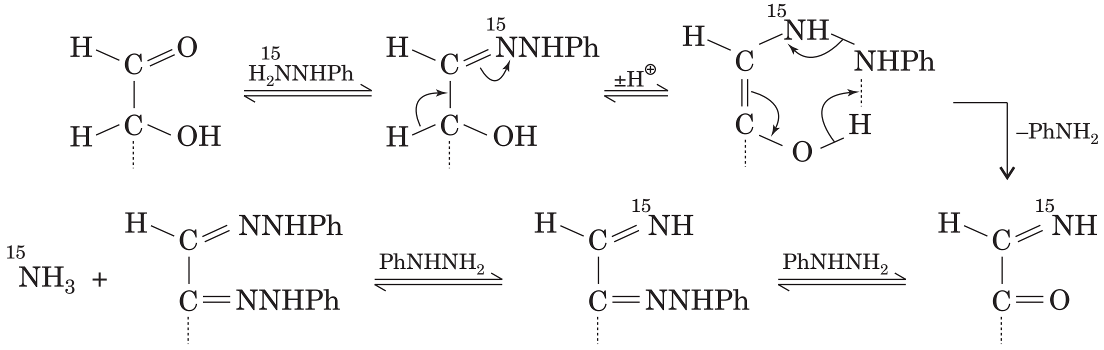
1. From aldose The aldose reacts with the first equivalent of phenylhydrazine to form the corresponding phenylhydrazone. It then undergoes **Amadori rearrangement** to yield a keto-imine. The imine then reacts with two molar equivalents of phenylhydrazine to yield an osazone.



2. From ketose In this case also, a phenylhydrazone is formed first. It then undergoes *Amadori rearrangement* to yield a keto-imine. The imine then reacts with two molar equivalents of phenylhydrazine successively to form an osazone.

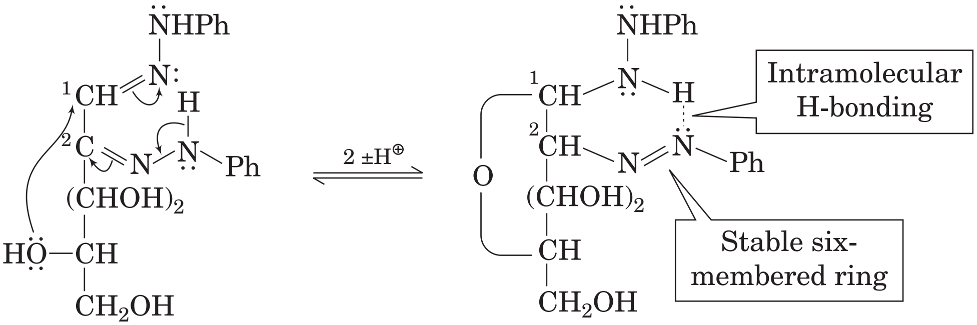


Proof of the mechanism The mechanism is supported by the observation that when phenylhydrazone prepared by the reaction of the aldose glucose with 15N labelled phenylhydrazine is treated with ordinary phenylhydrazine, unlabelled osazone is obtained accompanied by the expulsion of labelled ammonia ($^{15}NH_3$).



Reason for the involvement of the first two carbons in osazone formation The mechanism for osazone formation does not explain why only the first two carbon atoms should be involved. At first sight, it might have been expected that the Amadori rearrangement could carry on down the chain to yield a hexaphenylhydrazone. From spectroscopic studies (IR and UV) it has been establised that the resulting osazone remains in the following structure (I) which is stabilized by intramolecular H-bonding (chelation) involving the two

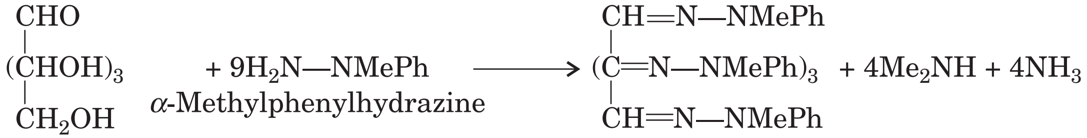
N atoms and because of such chelation, osazone formation does not proceed beyond two carbon atoms.



An osazone

I

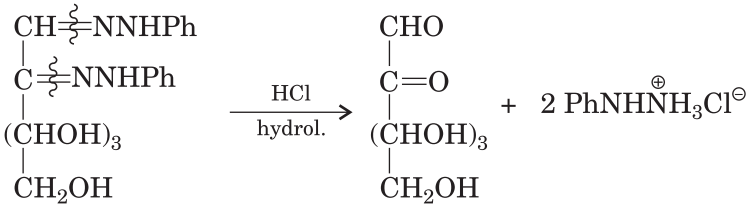
This explanation is further supported by the observation that unsymmetrically disubstituted hydrazines (e.g., α-methylphenylhydrazine) which cannot form osazones capable of chelation, react, further with aldoses giving alkazones in which osozone formation proceeds along the whole carbon chain of the sugar.



$$\begin{array}{c} CHO \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} + 9H_2N{-}NMePh \longrightarrow \begin{array}{c} CH{=}N{-}NMePh \\ | \\ (C{=}N{-}NMePh)_3 \\ | \\ CH{=}N{-}NMePh \end{array} + 4Me_2NH + 4NH_3$$

An aldopentose α-Methylphenylhydrazine An alkanes

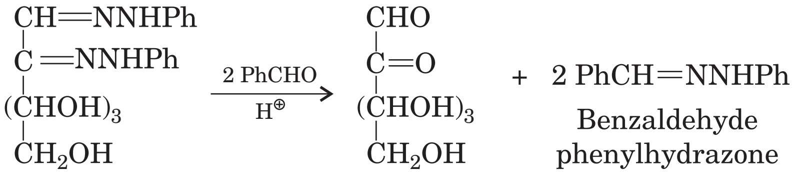
Characterists of osazones Osazones are bright yellow crystalline solids with sharp melting points and are, therefore, used to characterise the sugars. When they are hydrolyzed with hydrochloric acid, both the phenylhydrazino groups are eliminated to form a dicarbonyl compound known as *osone*. Glucosazone, for example, forms glucosone.



$$\begin{array}{c} CH{=}NNHPh \\ | \\ C{=}NNHPh \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} \xrightarrow[\text{hydrol.}]{HCl} \begin{array}{c} CHO \\ | \\ C{=}O \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} + 2\,PhNH\overset{\oplus}{N}H_3Cl^{\ominus}$$

An osazone An osone

A more convenient method of obtaining osone is to treat the osazone with benzaldehyde; benzaldehyde phenylhydrazone in precipitated, leaving the osone in solution. When osones are allowed to react with phenylhydrazine in the cold, osazones are obtained.

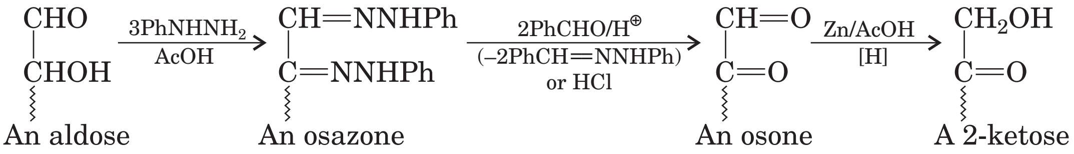


$$\begin{array}{c} CH{=}NNHPh \\ | \\ C{=}NNHPh \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} \xrightarrow[H^{\oplus}]{2\,PhCHO} \begin{array}{c} CHO \\ | \\ C{=}O \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} + 2\,PhCH{=}NNHPh$$

Benzaldehyde phenylhydrazone

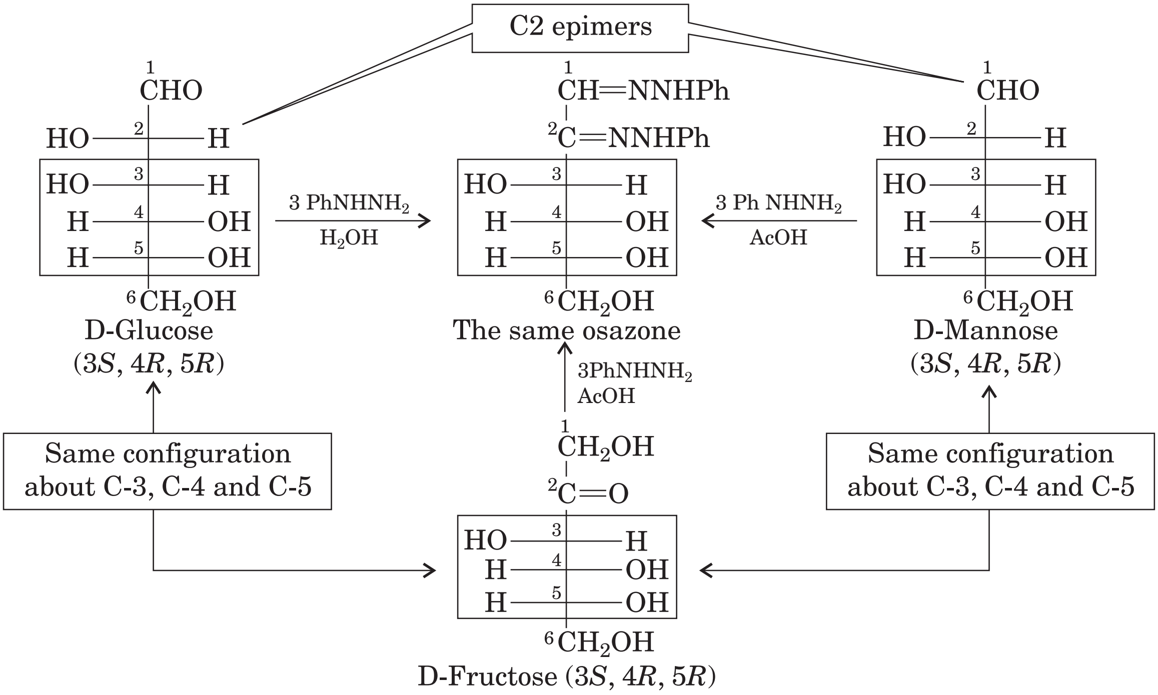
An osazone An osone

An aldose may be converted into a 2-ketose through the formation of an osazone as follows:



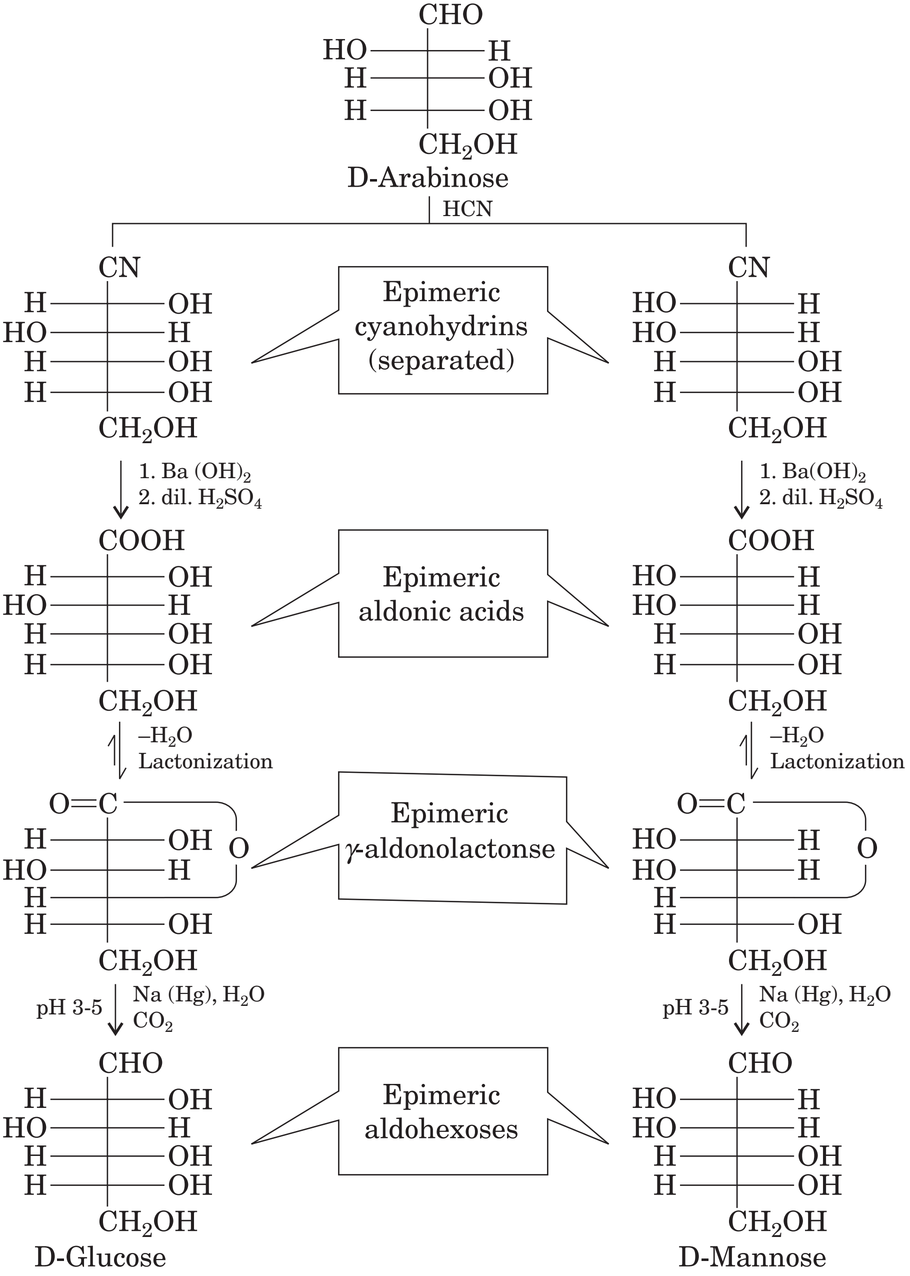
In the final step, the more reactive —CHO group of the osone is preferentially reduced to yield a 2-ketose.

D-glucose, D-mannose and D-fructose yield the same osazone on reaction with excess of phenylhydrazine Osazone formation destroys the chirality centre at C-2 but does not affect other chirality centres. Therefore, aldohexoses which are C-2 epimers (i.e., having the same configurations about C-3, C-4 and C-5 except C-2) form identical osazones. Since D-glucose and D-mannose are C-2 epimers, they form the same osazone. Again, a ketohexose which has the same configuration about C-3, C-4 and C-5 as its related aldohexose gives the same osazone. D-Fructose and D-glucose have the same configuration about C-3, C-4 and C-5. Consequently, D-fructose, D-glucose and D-mannose all form the same osazone.

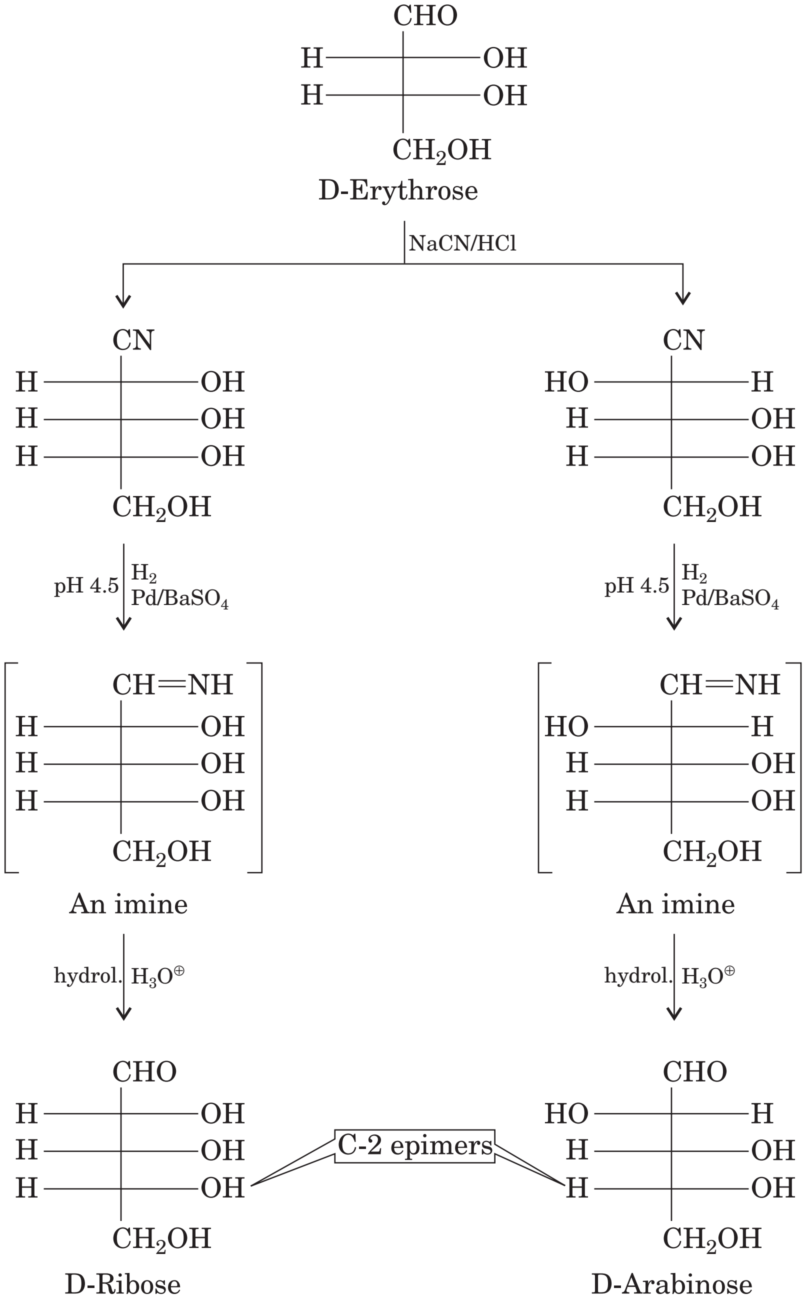


9.2.7 Lengthening the Carbon Chain of Aldoses

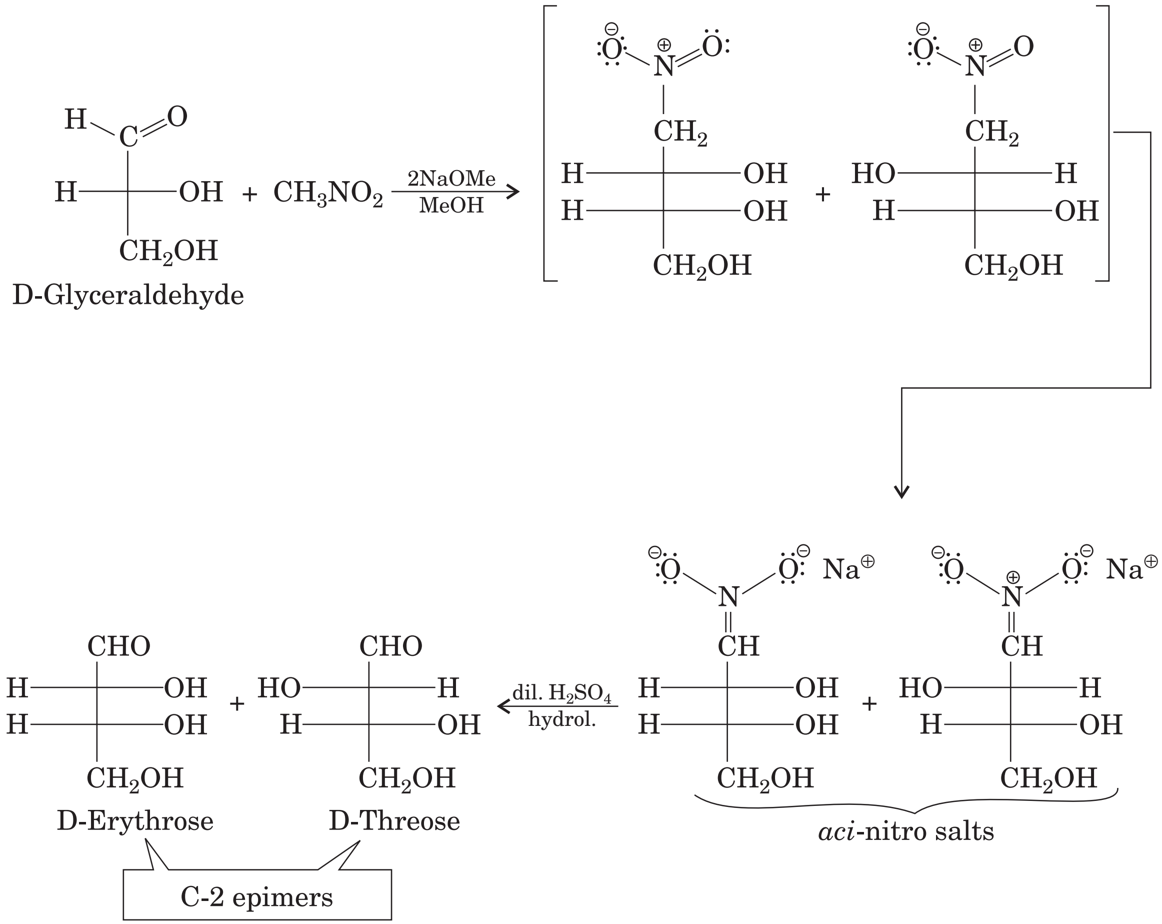
1. Kiliani–Fischer synthesis Heinrich Kiliani discovered in 1885 that an aldose can be converted to the epimeric aldonic acids having one additional carbon through the addition of hydrogen cyanide that leads to the formation of two epimeric cyanohydrins (due to formation of a new chirality center) followed by their hydrolysis. Because these epimers are diastereoisomers, they are typically formed in different amounts through the transition states of different energy. Fischer later synthesized aldoses by reducing aldonolactones obtained from aldonic acids. This method for lengthening the carbon chain of an aldose is called the *Kiliani–Fischer synthesis*. The process can be illustrated with the synthesis of D-glucose and D-mannose from D-arabinose (an aldopentose).



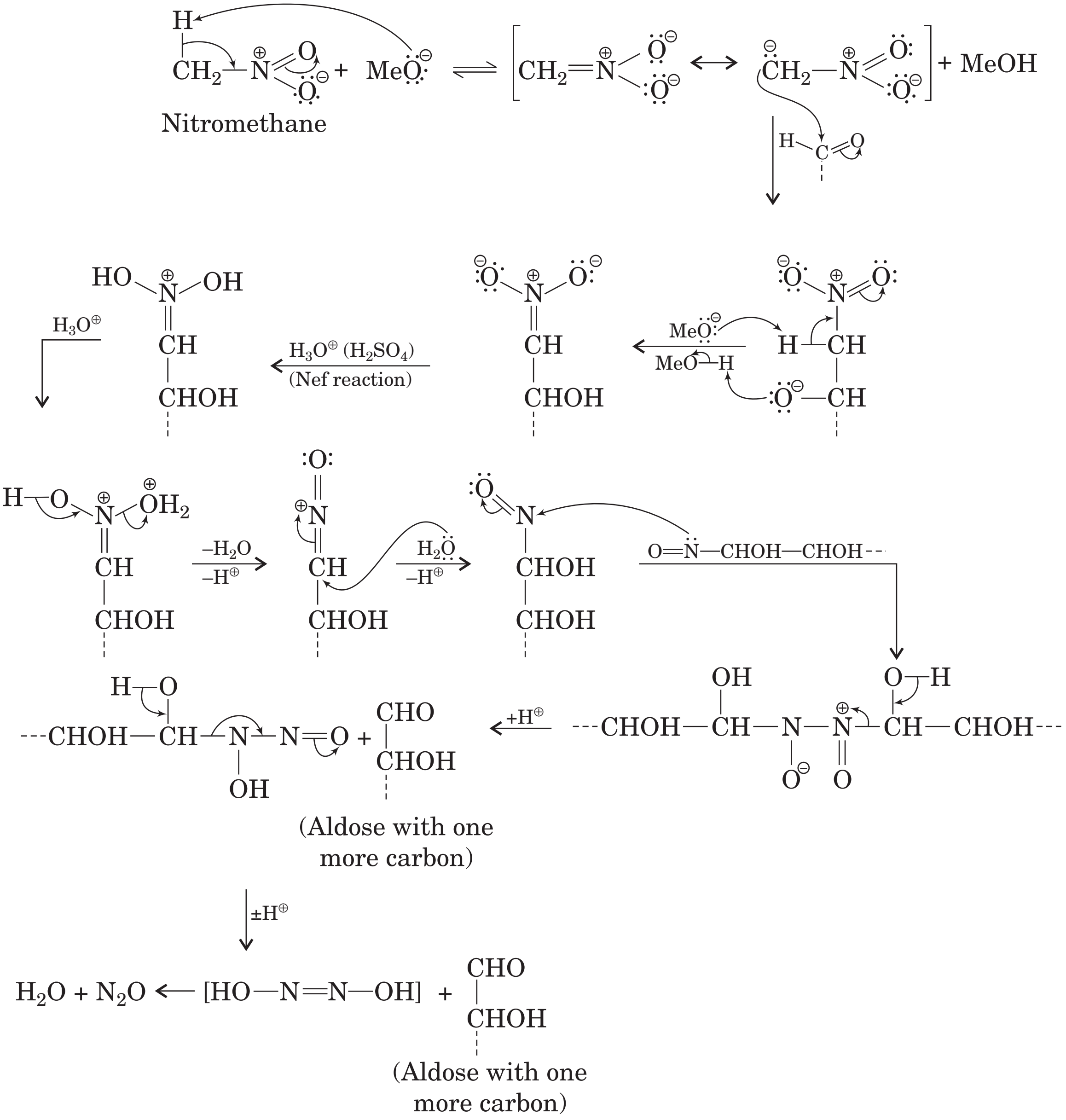
Modification of the Kiliani-Fischer synthesis The present-day modification of the Kiliani–Fischer synthesis involves catalytic hydrogenation of the epimeric cyanohydrins by the partially deactivated palladium catalyst. The intermediate imines are finally hydrolyzed to yield aldoses. The process can be illustrated with the synthesis of D-ribose and D-arabinose from D-erythrose.



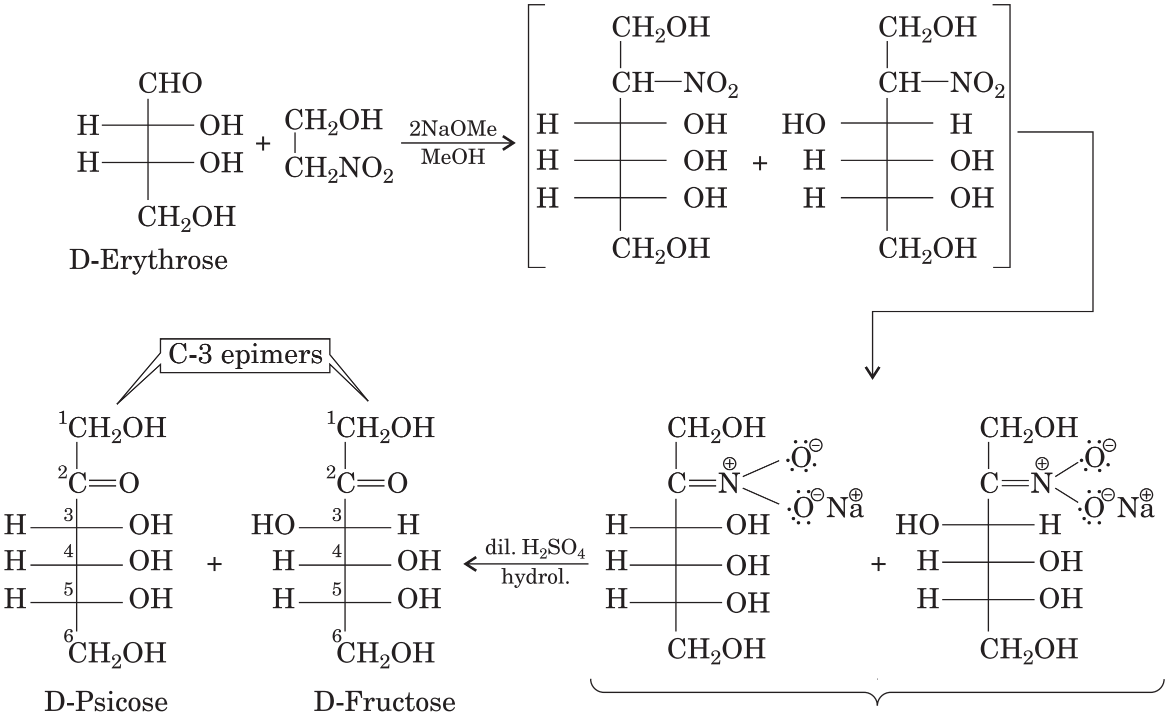
2. Sowden synthesis The Sowden method for stepping up of aldoses involves reaction with nitromethane in the presence of NaOMe/MeOH followed by hydrolysis of the salt of the *aci-nitro* intermediate (the *Nef reaction*). For example, D-glyceraldehyde may be converted into D-erythrose and D-threose as follows:



Mechanism for the reaction

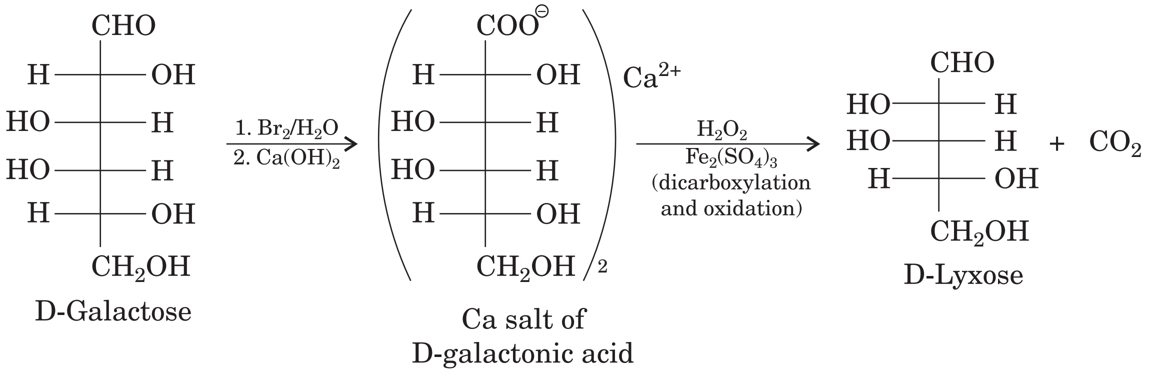

Nitromethane
+ MeOH
H₃O⊕
H₃O⊕ (H₂SO₄)
(Nef reaction)
–H₂O
–H⊕
H₂O
–H⊕
+H⊕
(Aldose with one more carbon)
±H⊕
H₂O + N₂O ⟵ [HO—N═N—OH] +
(Aldose with one more carbon)

An aldose can also be stepped up to a ketone containing two more carbon atoms using the above procedure except that 2-nitroethanol is used instead of nitromethane. For example, D-erythrose can be converted into D-psicose and D-fructose as follows:

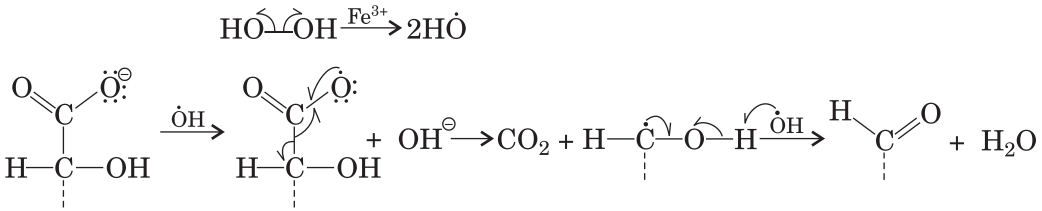


9.2.8 Shortening the Carbon Chain of Aldoses

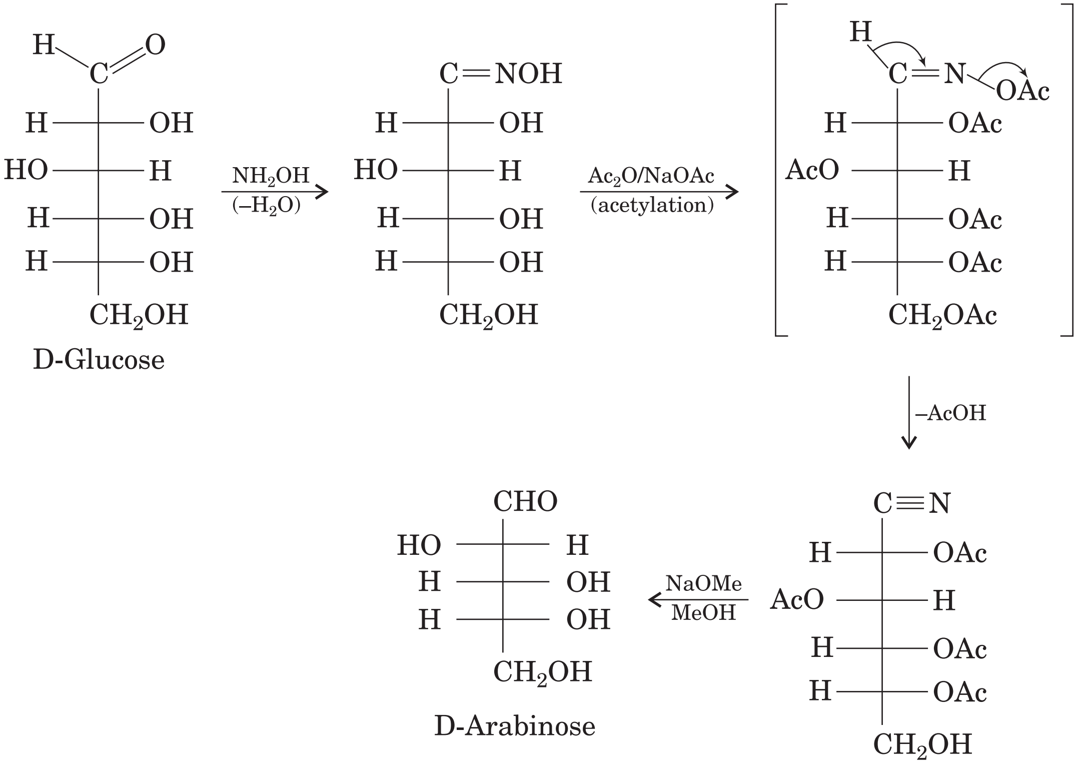
1. The Ruff Degradation The Ruff degradation shortens an aldose chain by one carbon atom. It is the original aldehyde carbon that is lost and a new —CHO group is created at what was C-2 in the starting sugar. In this process, the aldose is first oxidized to aldonic acid by bromine-water. The aldonic acid is then converted into its calcium salt by treating with calcium hydroxide and finally the calcium salt is treated with ferric sulphate and hydrogen peroxide to cause decarboxylation and oxidation of what was the C-2 carbon. D-Galactose, for example, may be converted into D-lyxose as follows:



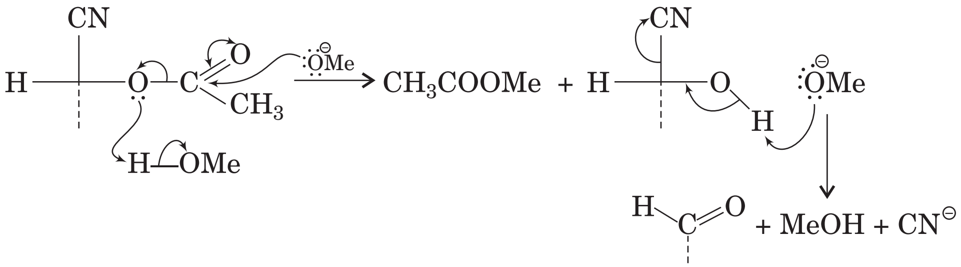
The plausible mechanism for decarboxylation and oxidation of C-2 is as follows:



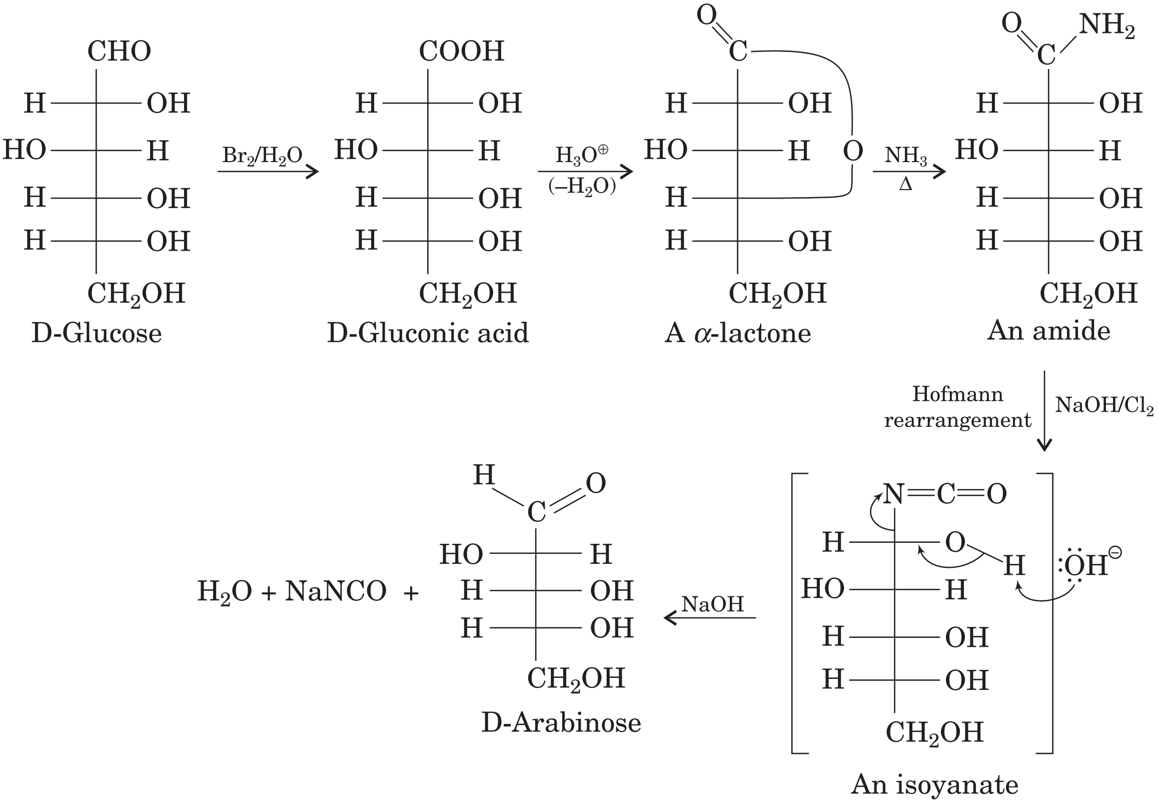
2. The Wohl degradation The Wohl degradation, an alternative to the Ruff degradation, is nearly the reverse to the Kiliani–Fischer synthesis. This method can be used to convert an aldose into another aldose with one less carbon atom. In this process, the aldose is first converted into its oxime. The oxime is then treated with Ac_2O/NaOAc to yield a completely acetylated oxime which readily loses a molecule of acetic acid to form a nitrile. The nitrile is finally treated with NaOMe in methanol to yield the next lower aldose. When D-glucose, for example, is subjected to the Wohl degradation, D-arabinose is obtained.



In the final step, the acetates undergo transesterification to yield methyl acetate freeing all the sugar –OH groups. This is followed by loss of a molecule of hydrogen cyanide.

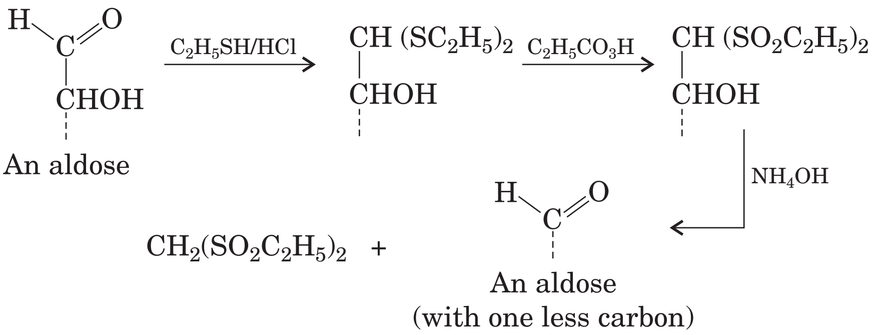


3. The Weerman degradation This degradation method is used to degrade aldose to another aldose with one less carbon atom. The first step of the Weerman degradation involves oxidation of the aldose with bromine-water to form the corresponding aldonic acid. When the aldonic acid is acidified, a γ-lactone is obtained. The lactone is then treated with ammonia to yield an amide. The amide is finally allowed to react with Cl_2/NaOH (Hofmann rearrangement) to yield the new lower aldose. D-Glucose, for example, may be converted into D-arabinose (an aldopentose) as follows:



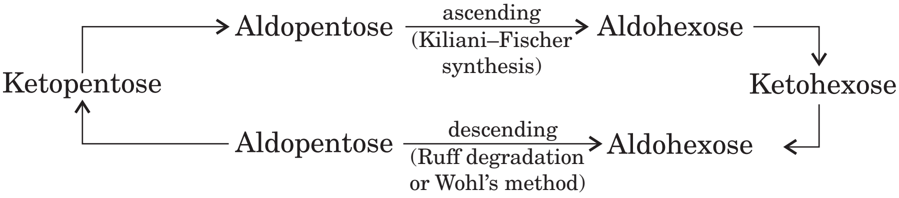
The α-hydroxyamide undergoes Hofmann rearrangement in the presence of Cl_2/NaOH to yield an isocyanate. Instead of being hydrolyzed, the isocyanate undergoes an elimination reaction to give the next lower aldose.

4. A recent method (Macdonald et al.) involving a thioacetal A more recent method of descending the sugar series involving a thioacetal in the first step may be outlined as follows:



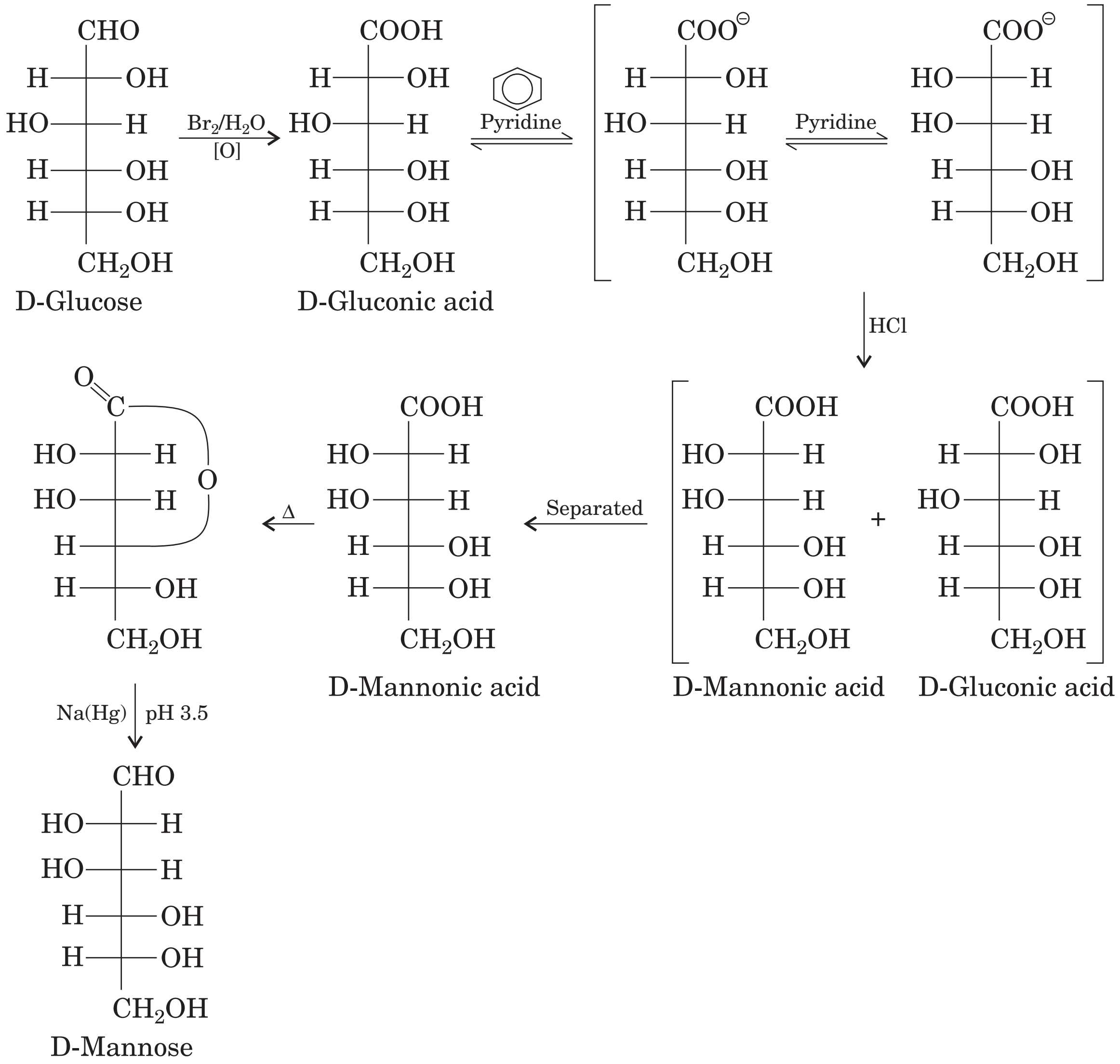
9.2.9 Ascending and Descending of Ketoses

Since the functional group in ketoses to be involved in the reaction for carrying out ascending or descending process is not present at the end of the carbon chain, common methods for ascending and descending of sugars cannot be directly applied to ketoses. Ascending and descending ketoses can, however, be carried out by converting a ketose into an aldose, descending (by the Kiliani–Fischer synthesis) or ascending (by Ruff or Wohl's method) that aldose, and then converting the resulting aldose into the corresponding ketose.

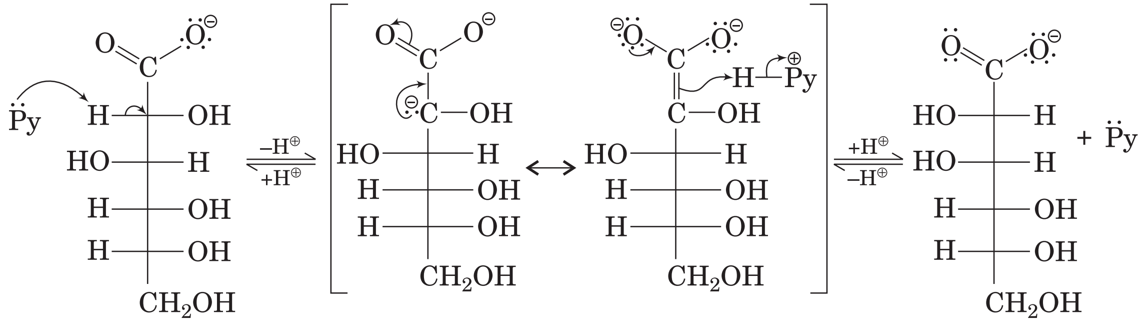


9.2.10 Conversion of an Aldose into its Epimer

In the presence of a tertiary amine, particularly in the presence of pyridine, an equilibrium is established between an aldonic acid and its C-2 epimer. This reaction is the basis of the best method for converting an aldose into its epimer because only the configuration of C-2 is affected. The aldose is first oxidized by bromine water to the aldonic acid, which is then treated with the base pyridine. From the equilibrium mixture thus formed, the epimeric aldonic acid having different physical characteristics is separated, and reduced (in the form of its lactone) to the epimeric aldose. For example, D-glucose can be converted to D-mannose as follows:

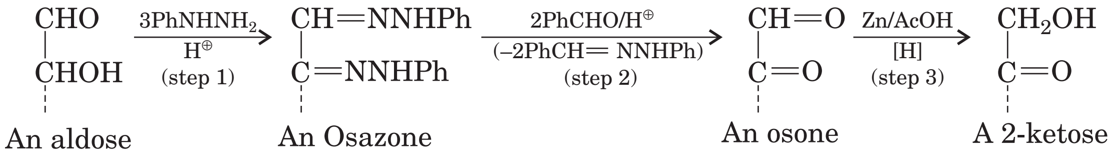


Mechanism for epimerization of aldonic acid (salt):



9.2.11 Conversion of an Aldose into a Ketose

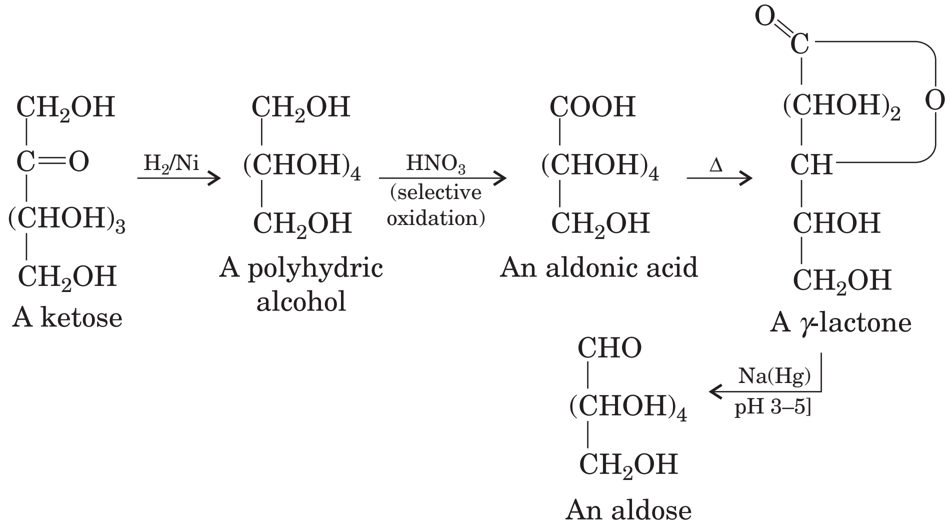
The conversion of an aldose into a ketose containing same number of carbon atoms involves formation of the osazone of the aldose by allowing it to react with excess of phenylhydrazine followed by treatment of the osazone with PhCHO in the presence of acid to yield an osone and then reduction of the osone with Zn/AcOH to yield a 2-ketose.



In step 2, the phenylhydrazino groups are transferred from osazone to PhCHO giving osone and a precipitate of benzaldehyde phenylhydrazone. In step 3, the more reactive aldehyde group is reduced preferentially to yield the ketose.

9.2.12 Conversion of a Ketose into an Aldose

The conversion of a ketose into an aldose involves the steps as follows. The ketose is first reduced to a, polyhydric alcohol by H_2/Ni. The polyhydric alcohol is then oxidized with HNO_3 to give a monocarboxylic acid (only one of the terminal —CH_2OH groups being oxidized). On warning, the acid is converted into a γ-lactone which, on reductive with sodium amalgam in faintly acid solution, is converted into an aldose.



When the ketone is reduced, two epimeric polyhydric alcohols may be formed due to formation of a new chirality centre. In practice, however, one of them predominates. Furthermore, when these two alcohols are oxidized, oxidation may take place at either end of the carbon chain, and hence the final product will be a mixture of four aldoses. However, these will not be present to the same extent.

9.2.13 Chemistry of D-(+)-Glucose (Dextrose, Grape-Sugar, Blood-Sugar)

The naturally occurring glucose is found to be dextrorotatory (hence the name *dextrose*) and the configuration of the last chirality centre (C-5) is found to be identical with that of D-glyceraldehyde. For this reason, naturally occurring glucose is often written as D-(+)-glucose. It is found in ripe grapes, honey and most sweet fruits. It is also a normal constituent of blood, and occurs in the urine of diabetics. Glucose is metabolized directly by the body.

9.2.13.1 Preparation of D(+)-glucose

D-Glucose can be prepared by hydrolyzing sucrose, starch or cellulose:

(i) From sucrose (cane sugar) D-Glucose is a constituent of the disaccharide called sucrose and can be obtained by hydrolyzing the latter with aqueous ethanolic solution of concentrated hydrochloric acid. An equimolar mixture of D-glucose and D-fructose is obtained. The acidic solution is neutralized and is then concentrated when the sparingly soluble D-glucose separates out as a crystalline solid. Fructose remains in the solution.

$$\underset{\text{Sucrose}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow[\Delta]{HCl} \underset{\text{D-Glucose}}{C_6H_{12}O_6} + \underset{\text{D-Fructose}}{C_6H_{12}O_6}$$

(ii) From starch Pure D-(+)-glucose is manufactured by heating starch with dilute hydrochloric acid under pressure.

$$\underset{\text{Starch}}{(C_6H_{10}O_5)_n} + nH_2O \xrightarrow[120°C;\ 2\text{–}3\ \text{atm}]{HCl} \underset{\text{D-Glucose}}{nC_6H_{12}O_6}$$

(iii) From cellulose When hydrolysed with fuming hydrochloric acid, cellulose gives D-glucose in 95–96% yield.

$$\underset{\text{Cellulose}}{(C_6H_{10}O_5)_n} + nH_2O \xrightarrow[\Delta]{HCl} \underset{\text{D-Glucose}}{nC_6H_{12}O_6}$$

9.2.13.2 Properties of D(+)-glucose

D(+)-Glucose, a colourless compound having m.p. 146°C, has a sweet taste, but is not as sweet as cane-sugar. It is a strong reducing agent, reducing both Fehling's solution and ammoniacal silver nitrate solution. When an aqueous solution of glucose is heated with NaOH, it turns brown. Glucose forms a cyanohydrin with hydrogen cyanide and an oxime with hydroxylamine (NH_2OH). All of these reactions are typical of aldehydes. However, when it is heated with phenyl hydrazine in acetic acid, the corresponding phenylhydrazone is not obtained and instead of that an osazone is obtained.

9.2.13.3 Structure of D-(+)-glucose

1. Elucidation of open-chain 'aldohexose' structure

That glucose possesses a polyhydroxyhexanal structure has been established on the basis of the following facts and conclusions therefrom:

(i) Elemental analysis and molecular weight determination confirm that the molecular formula of glucose is $C_6H_{12}O_6$.

(ii) When glucose is allowed to react with acetic anhydride, a penta-acetate is obtained. This observation indicates the presence of five hydroxyl group in the molecule. Organic compounds two –OH groups attached to a single carbon atom, i.e., the *gem*-dihydroxy compounds are unstable and usually lose a molecule of water $\left(\rangle C \langle^{OH}_{OH} \rightleftharpoons \rangle C{=}O + H_2O \right)$. Glucose is a stable molecule and does not eliminate a molecule of water on warming. This proves that the five hydroxyl groups in glucose are attached to five different carbon atoms (*vic*-dihydroxy compounds are thermally stable).

(iii) Reduction of glucose with H_2/Ni or $NaBH_4$ yields a hexahydric alcohol, sorbitol (glucitol) which produces *n*-hexane when reduced with hydroiodic acid and red phosphorus.

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \xrightarrow[\text{or } NaBH_4/H_2O]{H_2/Ni} \underset{\text{Sorbitol}}{C_6H_{14}O_6} \xrightarrow[100°C]{\text{Red P/HI}} \underset{n\text{-Hexane}}{CH_3(CH_2)_4CH_3}$$

This observation suggests that the six carbon atoms in glucose remain in a straight chain (C—C—C—C—C—C).

(iv) Glucose forms an oxime with hydroxylamine and a cyanohydrin with hydrocyanic acid. These reactions indicate that glucose contains a carbonyl group, i.e., it is either an aldehyde or a ketone.

(v) Glucose undergoes oxidation to yield a pentahydroxy acid ($C_6H_{12}O_7$) having the same number of C-atoms by the mild oxidizing agent like bromine-water. Also, glucose reduces Tollens' and Fehling's reagent. These are characteristic reactions of an aldehydic (—CHO) group. Therefore, glucose is an aldehyde and not a ketone. Since the six carbon atoms form a consecutive unbranched chain, the —CHO group must be present at one end of the chain.

(vi) Further oxidation of the pentahydroxy acid with HNO_3 produces a dicarboxylic acid ($C_6H_{10}O_8$). This indicates the presence of a primary alcoholic group (—CH_2OH) in the molecule because oxidation occurs with the loss of two hydrogens and gain of one oxygen.

On the basis of the foregoing reactions, the structure of glucose may be written as follows:

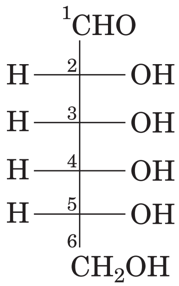
$$HO\overset{6}{C}H_2\overset{5}{C}HOH\overset{4}{C}HOH\overset{3}{C}HOH\overset{2}{C}HOH\overset{1}{C}HO$$

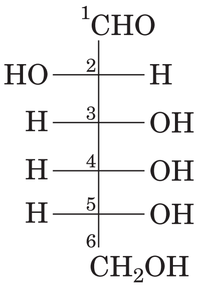
Number of stereoisomers There are four dissimilar asymmetric carbon atoms (C-2, C-3, C-4 and C-5) in the open-chain structure of glucose. Therefore, $2^4 = 16$ stereoisomers are possible.

2. Determination of the configuration of D-(+)-glucose (Fischer's proof)

Emil Fischer started his investigations on the stereochemistry of (+)-glucose in 1888 and after three years he succeeded in determining the correct configurations of all the chirality centres in the molecule. At that time the question of absolute configurations of the asymmetric carbon atoms were not settled and the study of stereochemistry was largely based on the stereochemistry of an asymmetric centre with the arbitrarily assigned stereochemistry of D- and L-glyceraldehyde. (+)-Glucose could have any one of the sixteen possible configurations (stereoisomers) of which eight must be of D-series and eight must be of L-series. Fischer arbitrarily decided that the relative configuration of C-5 asymmetric centre of natural (+)-glucose was like D-glyceraldehyde, i.e., the natural glucose is D-(+)-glucose. He carried out his investigations on the basis of this assumption.

Now, (+)-glucose could have any one of the following eight configurations (I–VIII) in which C-5 carried the –OH on the right.


I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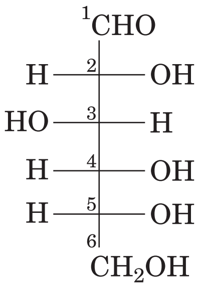
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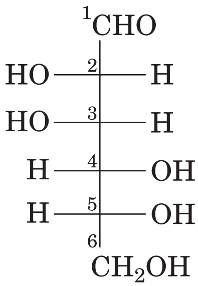
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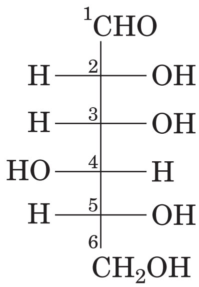
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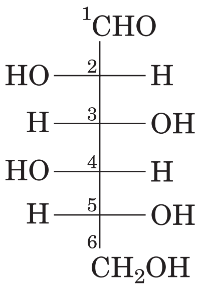
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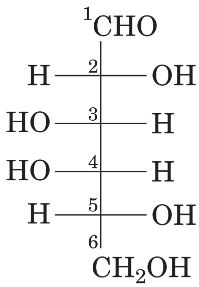
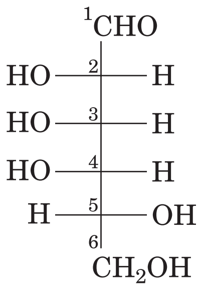
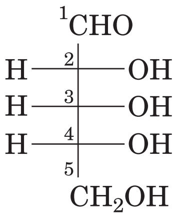

VII

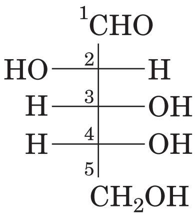

VIII

The aldopentose which has been considered in the Fischer's proof is (–)-arabinone. It is also assumed to be of D-series. Hence, out of eight possible configurations only four

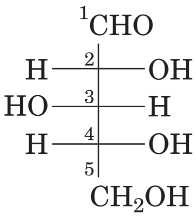
(IX–XII) in which C-4 carried the –OH on the right have been considered and (–)-arabinose could have any one of these configurations.



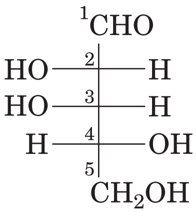
IX



X



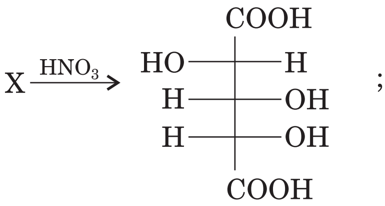
XI



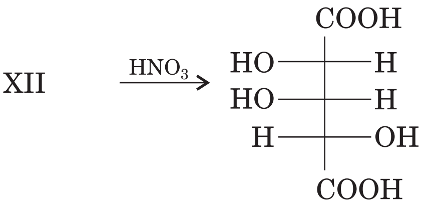
XII

Fischer's proof was based on the reasonings as stated below:

1. When (–)-arabinose is oxidized by nitric acid, it yields on optically active dicarboxylic acid. Optically active diacid may be obtained from X and XII, while *meso* diacid may be obtained from IX and XI.



Optically active
(no element of symmetry)



Optically active
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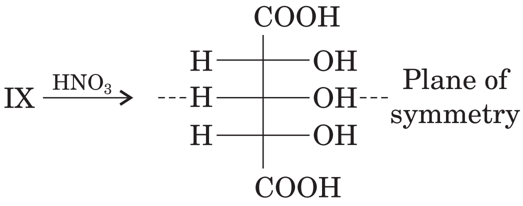
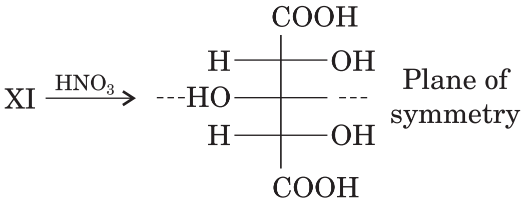


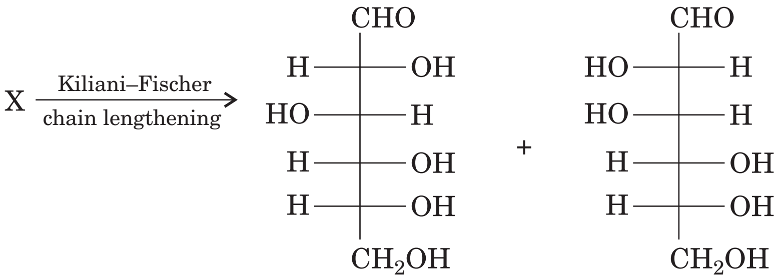
Optically inactive
(a *meso* compound)



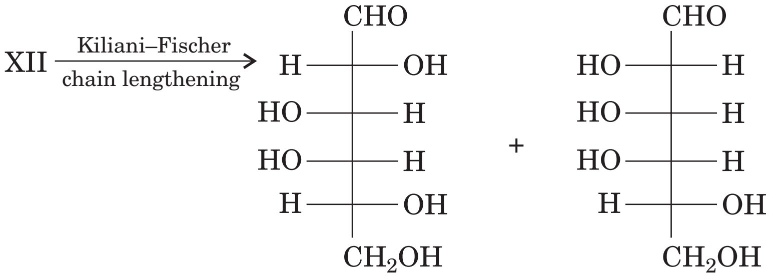
Optically inactive
(a *meso* compound)

   (–)-Arabinose is, therefore, X or XII. Hence, the –OH group on C-2 of this aldopentose must be on the left; the configuration of C-3 is yet to be settled.

2. (–)-Arabinose is converted into (+)-glucose and (+)-mannose by the Kiliani-Fischer synthesis. (+)-Glucose and (+)-mannose are therefore, C-2 epimers. If (–)-arabinose is X, (+)-glucose and (+)-mannose must be III and IV and if it is XII, (+)-glucose and (+)-mannose must be VII and VIII.

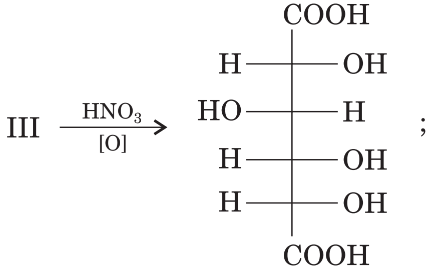


III IV



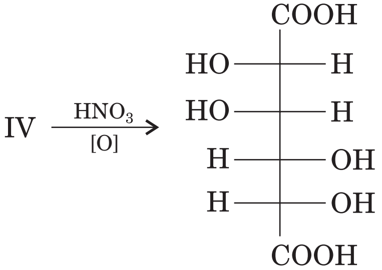
VII VIII

3. Optically active dicarboxylic acids are obtained when both (+)-glucose and (+)-mannose are oxidized by nitric acid. Optically active diacids may be obtained from the pair III and IV, while an optically active and an optically inactive diacid may be obtained from the pair VII and VIII.



Optically active
(no element of symmetry)

;



Optically active
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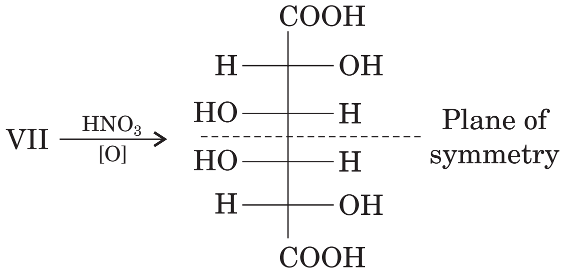
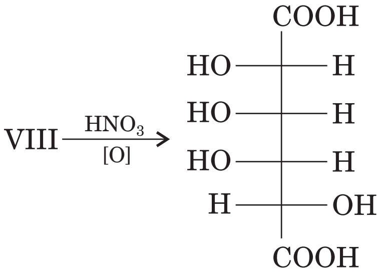


Optically inactive
(a *meso* compound)

;

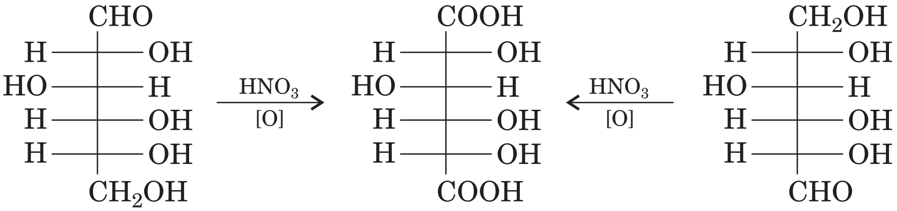


Optically active
(no element of symmetry)

Therefore, III and IV represent (+)-glucose and (+)-mannose. This means that the –OH on C-4 is on the right. [(–)-Arabinose must also have the same –OH (on C-3) on the right, and hence, has configuration X.]

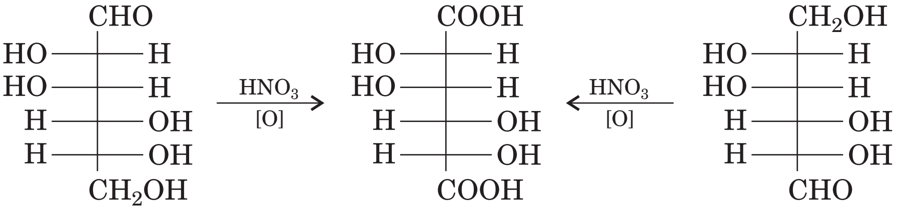
Now, it only remains to decide which compound has which configuration, i.e., whether III is (+)-glucose and IV is (+)-mannose or IV is (+)-glucose and III is (+)-mannose.

4. Oxidation of another hexose, (+)-gulose yields the same dicarboxylic acid, (+)-glucaric acid, as does oxidation of (+)-glucose. If we examine the two possible configurations for (+)-glucaric acid, IIIa and IVa, we see that only IIIa can be obtained from two different hexoses: from III and another aldohexose obtained by interchanging the terminal group —CH_2OH and —CHO of III, i.e., the enaniomer of V.



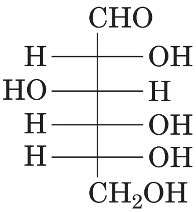
III IIIa Enantiomer of V i.e., (+)-gulose

The acid IVa can be obtained from just one aldohexose: from IV and this is because interchange of the terminals —CH_2OH and —CHO groups gives the same aldohexose.



IV IVa IV (rotated 180°)

It thus follows that (+)-glucaric acid has configuration IIIa, and therefore, that (+)-glucose has configuration III.



III

(+)-Glucose

[(+)-Mannose, of course, has configuration IV, and (–)-gulose (the enantiomer of the aldohexose used by Fischer) has configuration V.]

Although Fischer made an arbitrary choice that (+)-glucose was a D-sugar, later work by Bijvoet (1954) on the absolute configuration of naturally occurring (+)-glucose has confirmed that Fischer's assumption made in 1891 was correct, i.e., (+)-glucose is of D-variety (C-5 –OH is on right). According to the IUPAC nomenclature, the aldohexose form of D-(+)-glucose is named as (2*R*, 3*S*, 4*R*, 5*R*)-2,3,4,5,6-pentahydroxyhexanal.

3. Cyclic structure of D-(+)-glucose

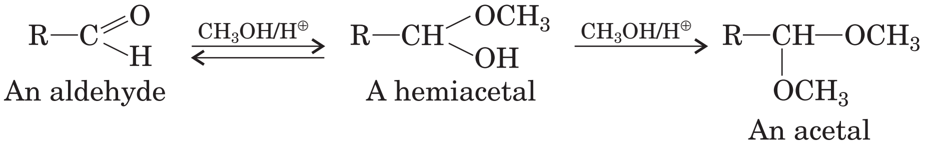
Although formulation of glucose as a straight-chain polyhydroxy aldehyde can explain many of its reactions, the facts that had still to be accounted for were the following:

(i) D-(+)-Glucose fails to undergo certain reactions typical of aldehydes. Glucose does not form sodium bisulphite addition product. Also, it cannot restore the pink colour of the Schliff's reagent.

(ii) D-(+)-Glucose exists in two isomeric forms, known as α-D-(+)-glucose (m.p. 146°C and specific rotation +112°) and β-D-(+)-glucose (m.p. 150°C and specific rotation +19°).

(iii) In aqueous solution, the two isomeric D-(+)-glucose undergo mutarotation. When crystals of ordinary D-(+)-glucose of m.p. 146°C are dissolved in water, the specific rotation gradually drops from an initial +112° to +52.7°. On the other hand, when crystals of D(+)-glucose of m.p. 150°C (obtained by crystallization at temperatures above 98°C) are dissolved in water, the specific rotation gradually rises from an initial +19° to +52.7°. The form with the higher positive rotation is called α-D-(+)-glucose and that with lower specific rotation β-D-(+)-glucose. The change in rotation of each of these to the equilibrium value is called mutarotation (*muta*, meaning change).

(iv) D-(+)-Glucose forms two isomeric methyl D-glucosides. Aldehydes react with alcohols in the presence of anhydrous HCl to form acetals. If methanol is used, the acetal contains two methyl groups.

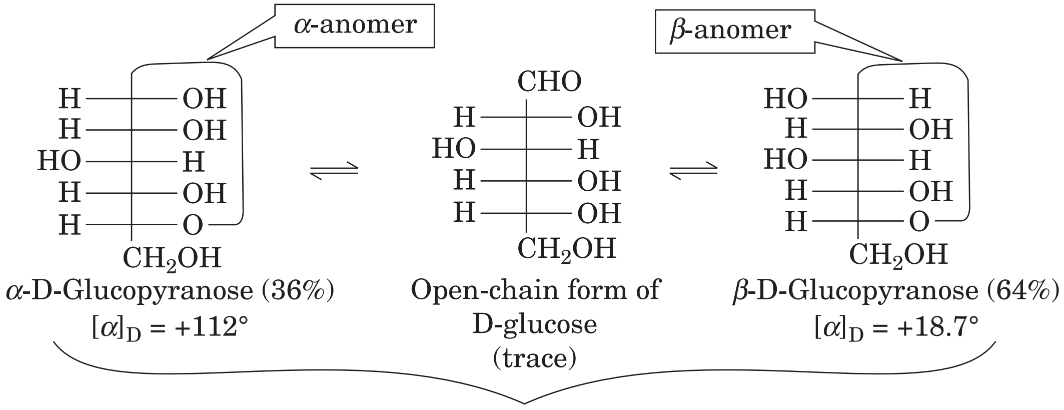


When D-(+)-glucose is treated with MeOH and HCl, the product, methyl D-glucoside contains only one —CH_3 group; yet it has properties similar to those a full acetal. It does not spontaneously revert to aldehyde and alcohol in the presence of water, but requires hydrolysis by aqueous acids. Furthermore, two of these mono-methyl derivatives of D-(+)-glucose are known, one with m.p. 165°C and specific rotation +158° and the other with m.p. 107° and specific rotation –33°. The isomer of higher positive rotation is called methyl α-D-glucoside and the other is called methyl β-D-glucoside. These glucosides do not undergo mutarotation and do not reduce Tollens' or Fehling's reagent.

(v) Esterification of glucose with Ac_2O produces two isomeric pentacetates and these do not react with NH_2OH.

To account for all these observations, a cyclic structure was proposed for D-(+)-glucose in which the —CHO group is not free, rather it forms a hemiacetal with the –OH group situated at C-5. In fact, glucose exists principally as two six-membered cyclic hemiacetals. A new asymmetric centre is created at C-1 by hemiacetal formation, and this leads to two diastereoisomeric forms of D-glucose called *α*-D-glucose or *α*-D-glucopyranose and *β*-D-glucose or *β*-D-glucopyranose (pyranose indicate sugar molecules which are structurally related to the six-membered heterocycle pyran). They differ only in the configuration at the hemiacetal carbon atom, the so-called **anomeric carbon**. Carbohydrate distereoisomers which differ only in the configuration of the anomeric C-atom are called **anomers**.

As hemiacetals, *α*- and *β*-D-(+)-glucose are readily hydrolyzed by water. Although the crystalline form of either isomer is quite stable, in aqueous solution either anomer is converted—via the open-chain form—into an equilibrium mixture containing both the cyclic isomers. This equilibration result from the ready opening and closing of the hemiacetal ring.



α-D-Glucopyranose (36%) $[\alpha]_D = +112°$

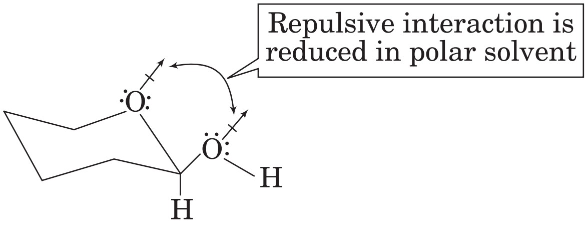
Open-chain form of D-glucose (trace)

β-D-Glucopyranose (64%) $[\alpha]_D = +18.7°$

Equilibrium mixture: $[\alpha]_D = +52.7°$

The process can be observed as a decrease in the optical rotation of the *α*-anomer (+112°) or an increase of the *β*-anomer (+18.7°) to the equilibrium value of +52.7°. At equilibrium about 64% of the *β*-anomer and 36% of the *α*-anomer are present. The conentration of the open-chain structure, however, is too low (less than 0.5%).

The relative amounts of the –OH group of cyclohexanol in the equatorial and axial position is 5.4:1, whereas the relative amounts of *β*- and *α*-D-glucose are 2:1. Due to stabilization of the *α*-anomer by electron delocalization involving transfer of some electron density from the sp^3 orbital of oxygen in the parallel σ^* antibonding orbital of the C—OH bond, the *α*-anomer is expected to be present as the major component (anomeric effect). But the reverse is true. In the highly polar solvent water, the anomeric effect is usually outweighed because this polar solvent stabilizes the more polar *β*-anomer by decreasing the dipole-dipole repulsive interaction. Also an equatorial –OH group is less crowded and better solvated by water through H-bonding than an axial one. [In a relatively less polar solvent such as methanol, the anomeric effect becomes much strong and as a result, the amount of the *α*-anomer increases. In fact, there is 50% of *α*-D-glucose in dry methanol.]



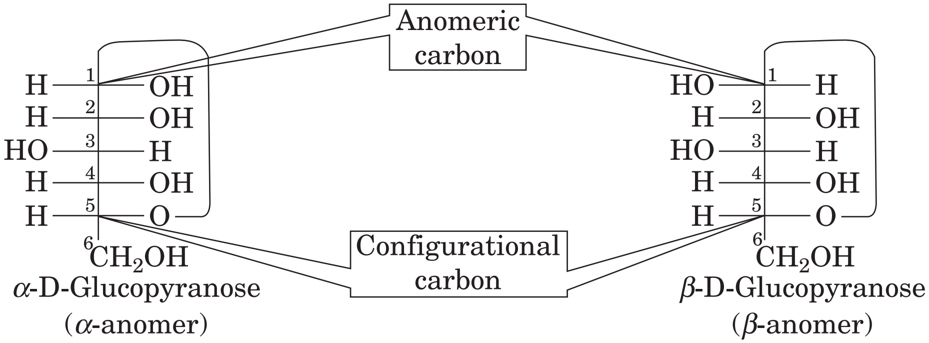
A D-Glucopyranoside

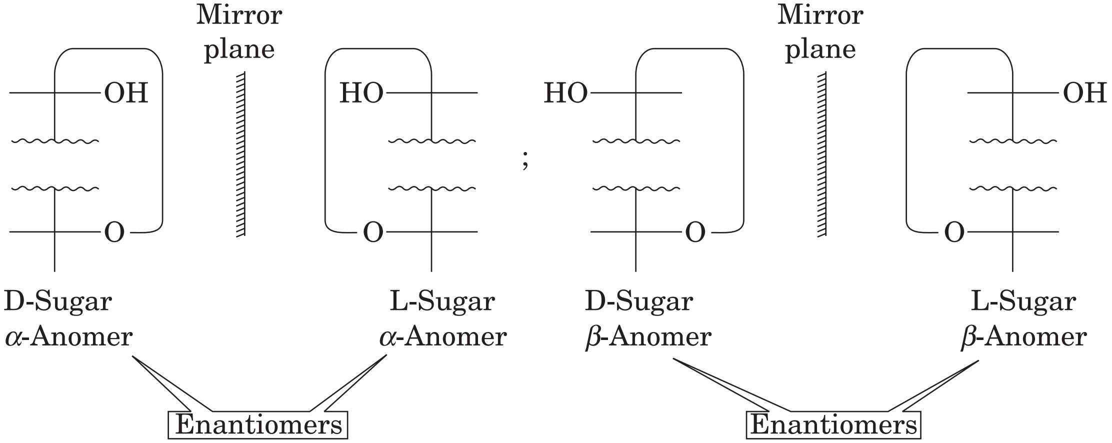
The typical aldehyde reactions of D-(+)-glucose – osazone formation, and reduction of Tollens' and Fehling's reagents – are, in fact, due to presence of a small amount of the open-chain form, which is replenished as fast as it is consumed. Since the concentration of the open-chain form is very low, certain easily reversible aldehyde reactions like bisulphite addition and the Schiff test do not take place.

The hydroxyl at C-4 in the open-chain form could also add to the aldehyde carbonyl to produce a hemiacetal with a five-membered ring. This does not take place to a significant degree with glucose because the hemiacetal with six-membered ring and many equatorial groups is more stable. The widely accepted view is that D-(+)-glucose in solution exists mainly as an equilibrium mixture of the α- and β-anomeric pyranoses, a small amount of the open-chain form together with small amounts of the α- and β-anomeric furanoses.

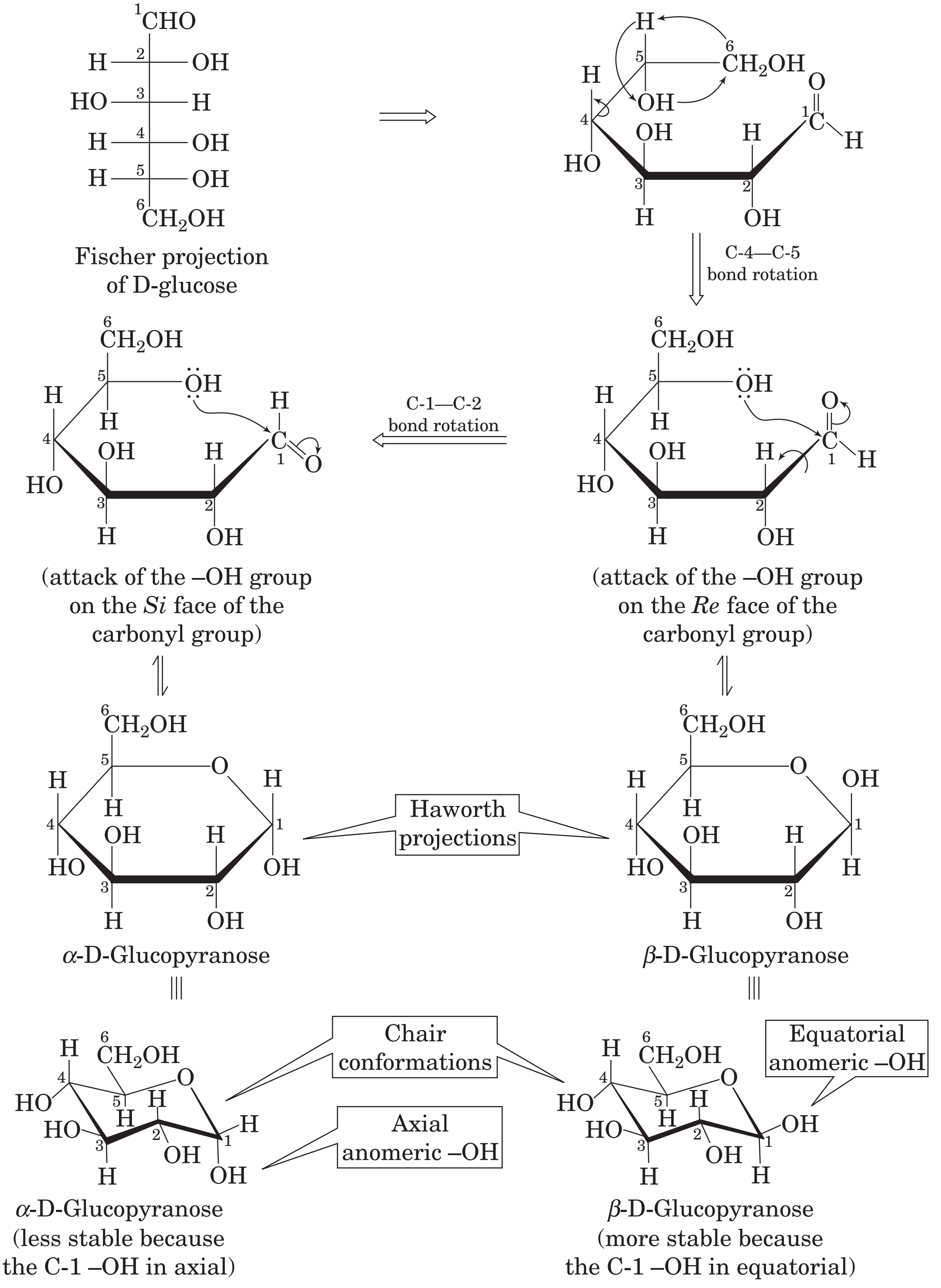
Naming of the cyclic hemiacetal forms of carbohydrates according to their five- or six-membered ring For naming a cyclic hemiacetal form of a carbohydrate, one has to start with a prefix derived from the name of the carbohydrate (for example, **gluco** for glucose, **manno** for mannose, etc.) followed by a suffix that indicates the type of the hemiacetal ring (**pyranose** for a six-membered ring and **furanose** for a five-membered ring). Thus, a six-membered cyclic hemiacetal form of D-glucose is called D-glucopyranose, a five-membered cyclic hemical form of D-ribose is called D-ribofuranose, a five-membered cyclic hemiacetal form of D-fructose is called D-fructofuranose, etc.

Designation of anomers on the basis of the location of the C-1 –OH group Anomers are designated with the Greek letters α and β. This nomenclature refers to the Fischer projection of the cyclic hemiacetal form of a carbohydrate, written with all carbon atoms in a straight vertical line and the C-1 carbon at the top. The anomer in which the hemiacetal –OH group (also called the anomeric –OH group) is on the same side of the Fischer projection as the oxygen at the configurational or reference carbon (the highest numbered asymmetric carbon used for specifying the D, L designation) is called the α-**anomer** and the anomer in which the hemiacetal –OH group is on the opposite side of the Fischer projection as the oxygen at the configurational or reference carbon is called the β-**anomer**.





To draw the cyclic hemiacetal forms of D-glucose both as Haworth projections and as chair conformations The cyclic hemiacetal forms of D-glucose as Haworth projections and as chair conformation can be drawn by the following operations. The Fischer projection of the molecule is first laid down over on its right side. The groups that were on the right in the Fischer projection are down in the cyclic structure and the groups that were on the left are up. C-5 and C-6 curl back away. The C-4—C-5 bond is then rotated so that the C-5 hydroxyl group can form a part of the ring. For a sugar of the D series, this rotation puts the terminal —CH_2OH group upward. The ring is then closed and the final hemiacetals are drawn in Haworth projections with the oxygen at the back right-hand corner, with C-1 at the far right. C-1 can be easily identified because it is the anomeric (hemiacetal) carbon—the only carbon bonded to two oxygens. The hydroxyl group on C-1 can be either up or down. The anomer with the anomeric –OH group down (*trans* to the terminal —CH_2OH group) is called the *α*-**(***alpha***) anomer**, while the other with the anomeric –OH group up (*cis* to the terminal —CH_2OH group) is called the *β*(*beta*) **anomer**. Both of these anomers are then drawn in stable chair conformations in which the anomeric carbon and the ring oxygen are in the same relative positions as they are in the preceding Haworth projections and the **up** and **down** groups are placed in axial or equatorial positions, as appropriate. All the ring substituents are equatorial in the *β*-anomer. Only the anomeric –OH group is axial in the *α*-anomer; all other substituents are equatorial.



Fischer projection of D-glucose

(attack of the –OH group on the *Si* face of the carbonyl group)

(attack of the –OH group on the *Re* face of the carbonyl group)

α-D-Glucopyranose

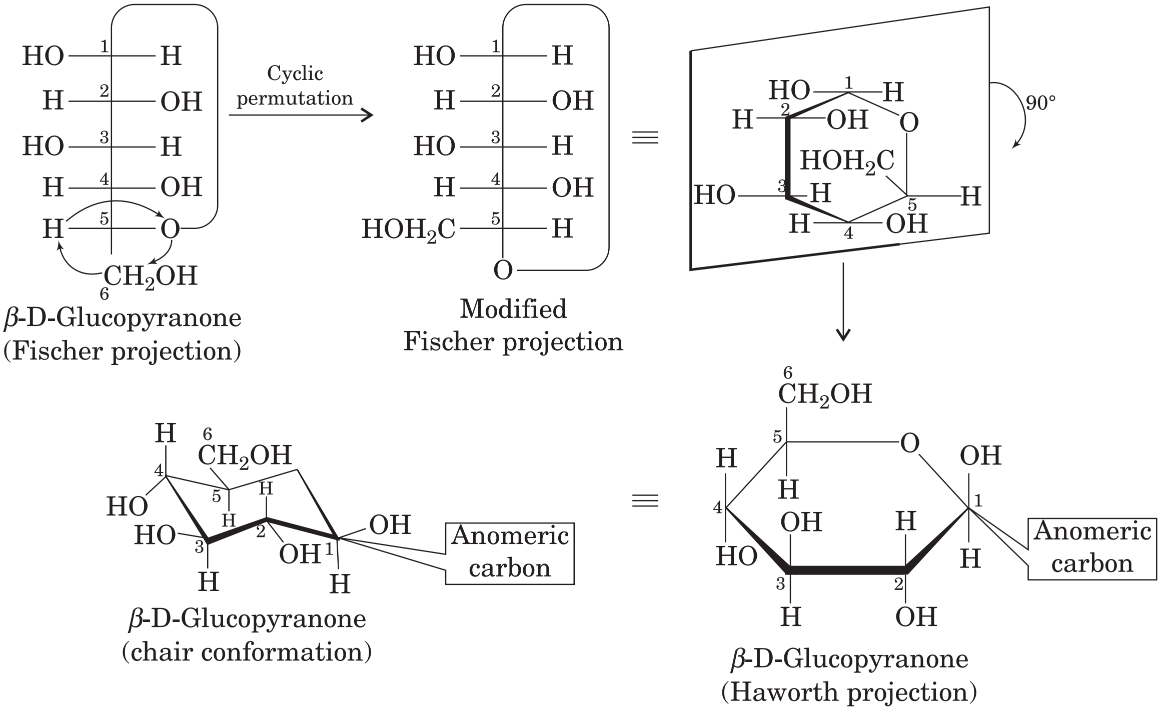
β-D-Glucopyranose

α-D-Glucopyranose (less stable because the C-1 –OH in axial)

β-D-Glucopyranose (more stable because the C-1 –OH in equatorial)

Conversion of the Fischer projection of β-D-glucopyranose into its chair conformation through Haworth projection The Fischer projection of β-D-glucopyranose is first redrawn in an equivalent Fischer projection in which the ring oxygen is placed in the down position. This is carried out by using a cyclic permutation of the groups on C-5 (an allowed manipulation of Fischer projection). The carbon backbone of this modified Fischer projection is imagined to be folded around a drum. Such an interpretation of the Fischer projection gives the structure in which the ring lies in a plane perpendicular to the page. When the plane of the ring is turned 90° so that the anomeric carbon is on the right and the ring oxygen is placed in the back right-hand corner, the substituents in up positions are those that are on the left in the Fischer projection and the substituents in down position are those that are on the right in the Fischer projection. This type of planar structure is called a Haworth projection. In a Haworth projection, the ring is drawn in a plane at right angles to the page and the positions of the substituents are indicated with up and down bonds. Finally, β-D-glucopyranose is drawn in a stable chair conformation (all substituents occupy equatorial positions) in which the anomeric carbon and the ring oxygen take up the same relative positions as they are in the preceding Howarth projection and the up and down substituents are placed in axial or equatorial positions, as appropriate.

Thus, the chair conformation of β-D-glucopyranone may be drawn from its Fischer projection *via* the Haworth conformation as follows:



β-D-Glucopyranone (Fischer projection)

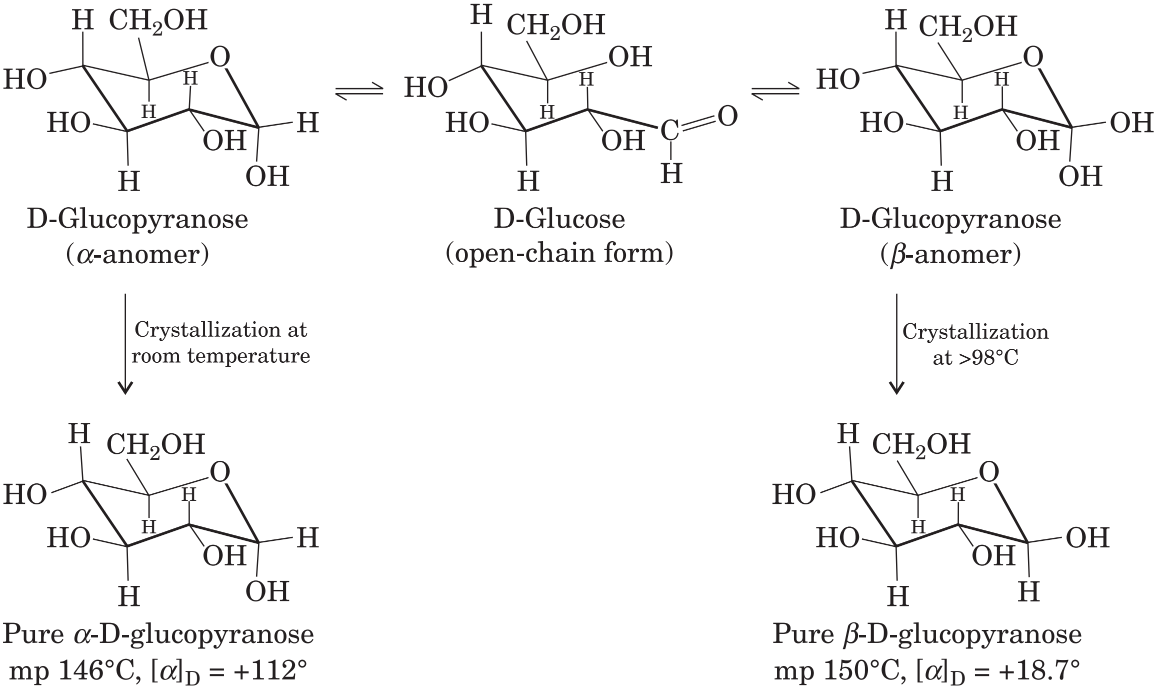
Modified Fischer projection

β-D-Glucopyranone (chair conformation)

β-D-Glucopyranone (Haworth projection)

[It has been established from X-ray crystallographic studies of a large number of carbohydrates that the six-membered pyranose ring of D-glucose, like substituted cyclohexanes, exists in chair conformation.]

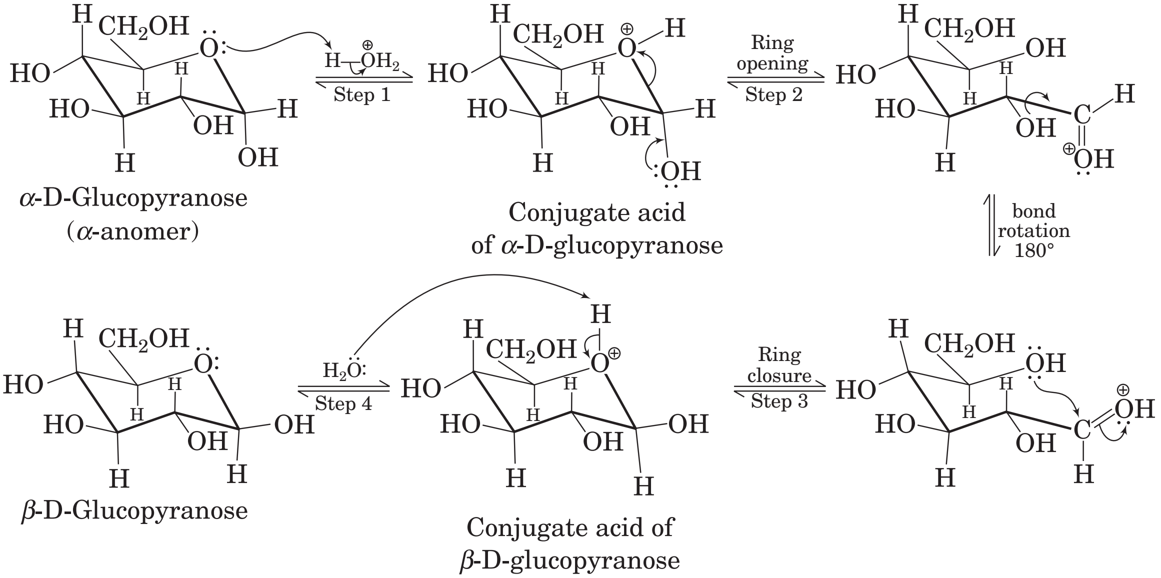
Isolation of the pure α-anomer (mp 146°C, $[\alpha]_D = +112°$) and β-anomer (mp 150°C, $[\alpha]_D = +18.7°$) of D-glucopyranone from its aqueous solution When glucose is crystallized from water at room temperature, pure crystalline α-D-glucopyranose is obtained and when glucose is crystallized from water letting the water to evaporate at a temperature >98°C, crystals of pure β-D-glucopyranose (the ordinary form of D-glucose) are obtained. In the solution, the two anomers remain in equilibrium through a very small amount of the open-chain form, and this equilibrium continues to supply more of the anomer that is crystallizing out of the solution at a particular temperature.



D-Glucose is the most abundant aldohexose in nature All the –OH substituents in the β-anomer of D-glucose or D-glucopyranose are equatorial. The axial positions are all occupied by hydrogens, which require very small space and therefore, this anomer experience little steric strain. No other aldohexose exists in such a strain-free conformation. For this reason, D-glucose is the most abundant aldohexose in nature.

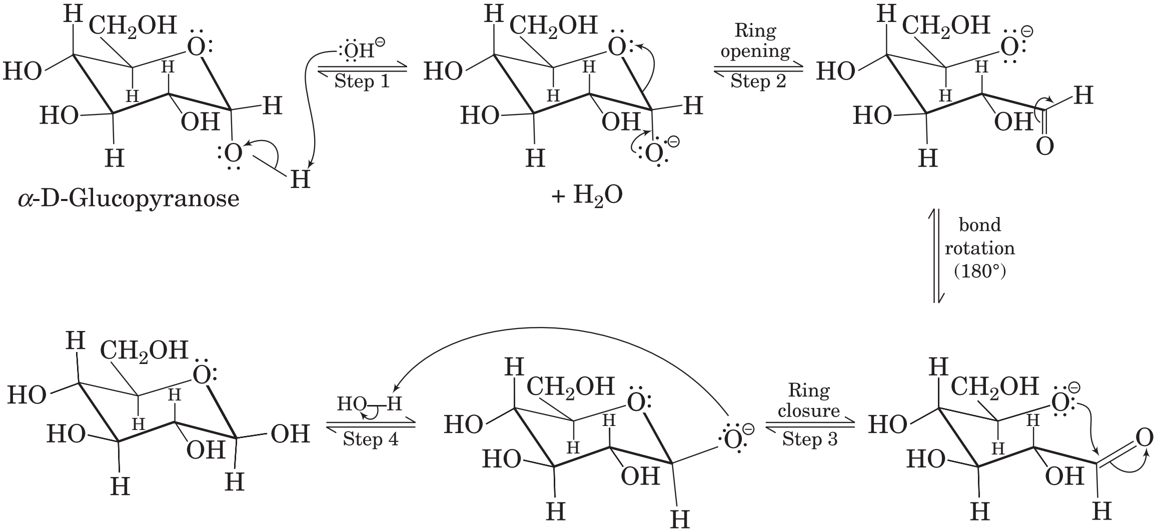
Mechanism of mutarotation Mutarotation is catalyzed by both acid and base. It also occurs even in pure water in which an acid-base catalyzed mechanism operates concertedly.

1. Mechanism for the acid-catalyzed mutarotation of D-glucopyranose



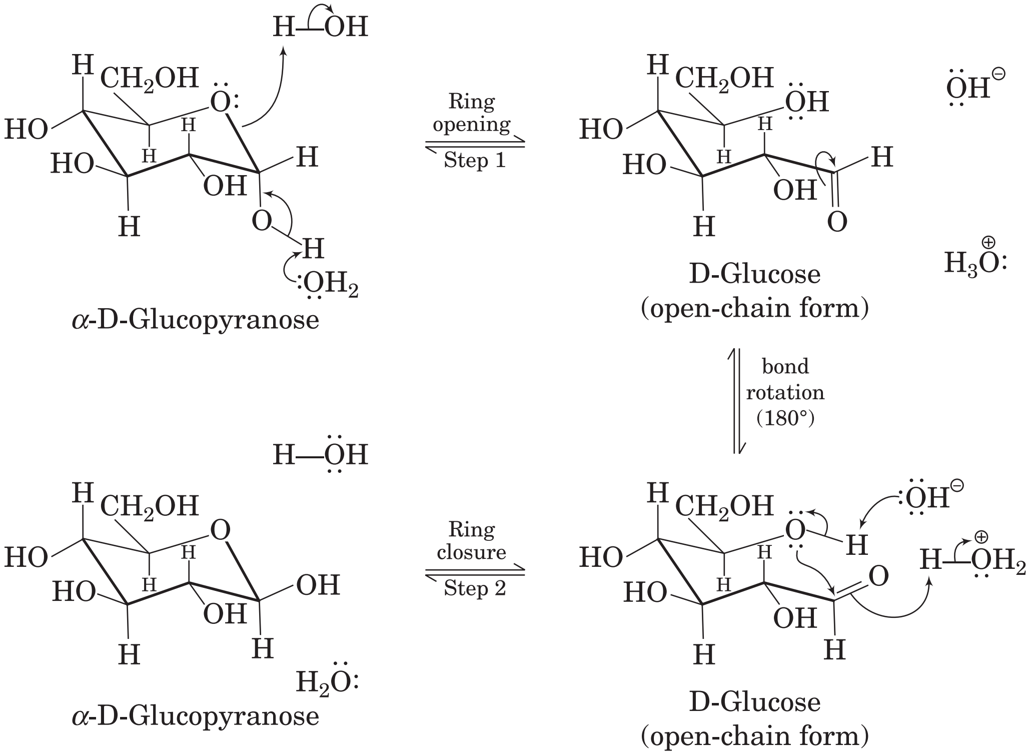
In step 1, the oxygen of the pyranose ring undergoes protonation by the acid catalyst. In aqueous solution, the acid catalyst is the hydroxonium ion. In step 2, the pyranose ring opens up by cleaving the bond between the anomeric carbon and the positively charged oxygen. This ring opening is facilitated by the release of electrons from the –OH group at the anomeric carbon and gives the conjugate acid of the open-chain form of D-glucose. In step 3, the conjugate acid of the open-chain form cyclizes through its bond rotated conformation to give the conjugate acid of *β*-D-glucopyranose. This cyclization is analogous to the acid-catalyzed nucleophilic addition to a carbonyl group. In step 4, the resulting conjugate acid transfers a proton to water to yield *β*-D-glucopyranose.

2. Mechanism for the base-catalysed mutarotation of D-glucopyranose



In step 1, the base takes up a proton to form the conjugate base of α-D-glucopyranose. In step 2, the pyranose ring opens up by cleaving the bond between the anomeric carbon and oxygen. In step 3, the conjugate base of the open-chain form cyclizes through its bond rotated conformation to give the conjugate base of β-D-glucopyranose and in step 4, the resulting conjugate base takes up a proton from water to yield β-D-glucopyranose.

3. Mechanism for mutarotation in water involving concerted attack by water (an amphiprotic solvent) as a base and as an acid



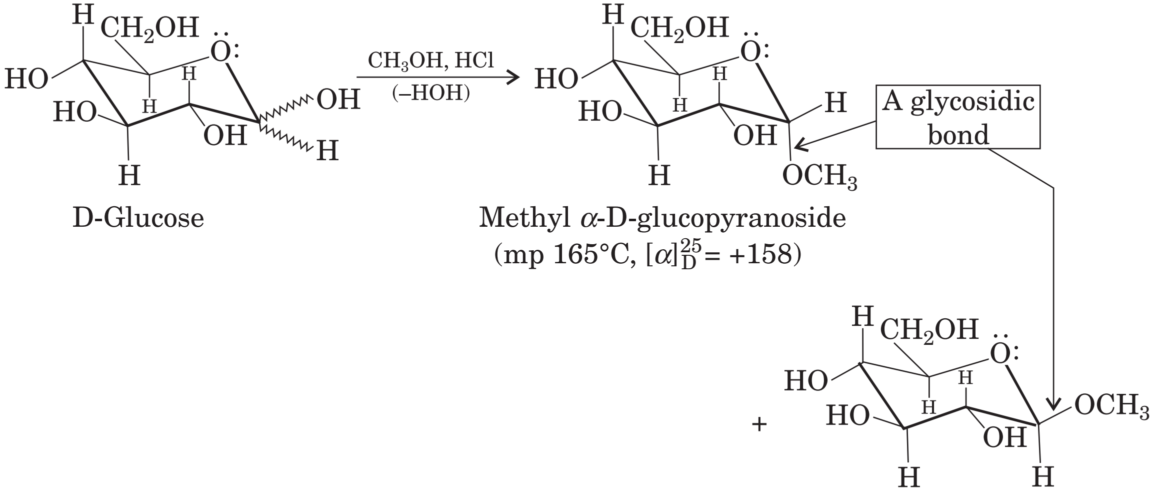
The opening of the cyclic hemiacetal in step 1 appears to a concerted process involving the simultaneous removal of a proton from the anomeric –OH group and donation of a proton to the ethereal oxygen atom. In step 2, ring closure takes place concertedly by simultaneously removal of a proton from C-5 –OH group and donation of a proton to the carbonyl oxygen atom. Since water being an amphiprotic solvent can act as both an acid and a base, mutarotation proceeds most readily by this mechanism in aqueous medium.

9.2.13.4 Glycosides

Most monosaccharides react with alcohols under acidic conditions to yield cyclic acetals. Such compounds are called *glycosides*. They are, in fact, some special types of acetals in which one of the oxygens of the acetal linkage is the ring oxygen of the pyranose or furanose. The bond between the anomeric carbon and the alkoxy oxygen is called a glycosidic bond. The group bonded to the anomeric carbon of a glycoside is called an *aglycone*. For example, the methoxy (—OCH_3) group is the aglycone in a methyl glycoside.

Glycosides are named by replacing the 'e' ending the sugar's name with 'ide'. Thus, the glycoside of glucose is a glucoside, the glycoside of ribose is a riboside, etc. Furthermore, if the glucoside is a six-membered ring, it is called glucopyranoside. Similarly, if riboside exists as a five-membered ring, it is called ribofuranoside.

Formation of glycosides When a small amount of gaseous hydrogen chloride is allowed to pass into a solution of D-(+)-glucose in methanol, a reaction occurs that results in formation of two anomeric methyl glycosides (acetals).



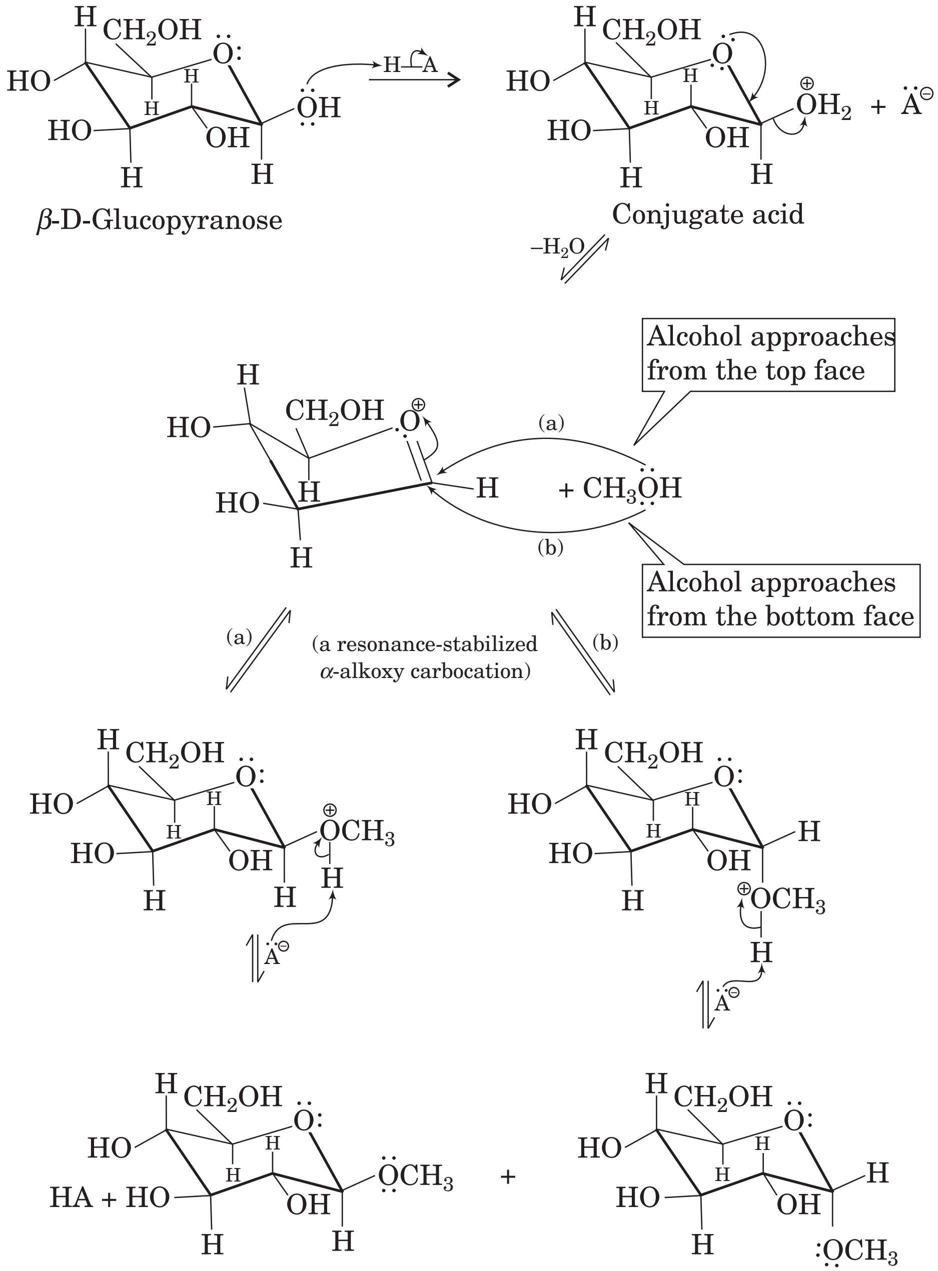
D-Glucose

Methyl α-D-glucopyranoside (mp 165°C, $[\alpha]_D^{25}$= +158)

Methyl β-D-glucopyranoside (mp 107°, $[a]_D^{25}$ = –33)

However, when 1% hydrochloric acid is added to a solution of D-glucose is methanol and the solution in allowed to stand at 0° (or at room temperature), methyl D-glucofuranosides are obtained.

Mechanism for the formation of glycosides The mechanism for the formation of methyl glucosides (starting arbitrarily with the β-anomer of D-glucopyranose may be outlined as follows:



β-D-Glucopyranose

Conjugate acid

Alcohol approaches from the top face

Alcohol approaches from the bottom face

(a resonance-stabilized α-alkoxy carbocation)

Methyl β-D-glucopyranoside (minor product)

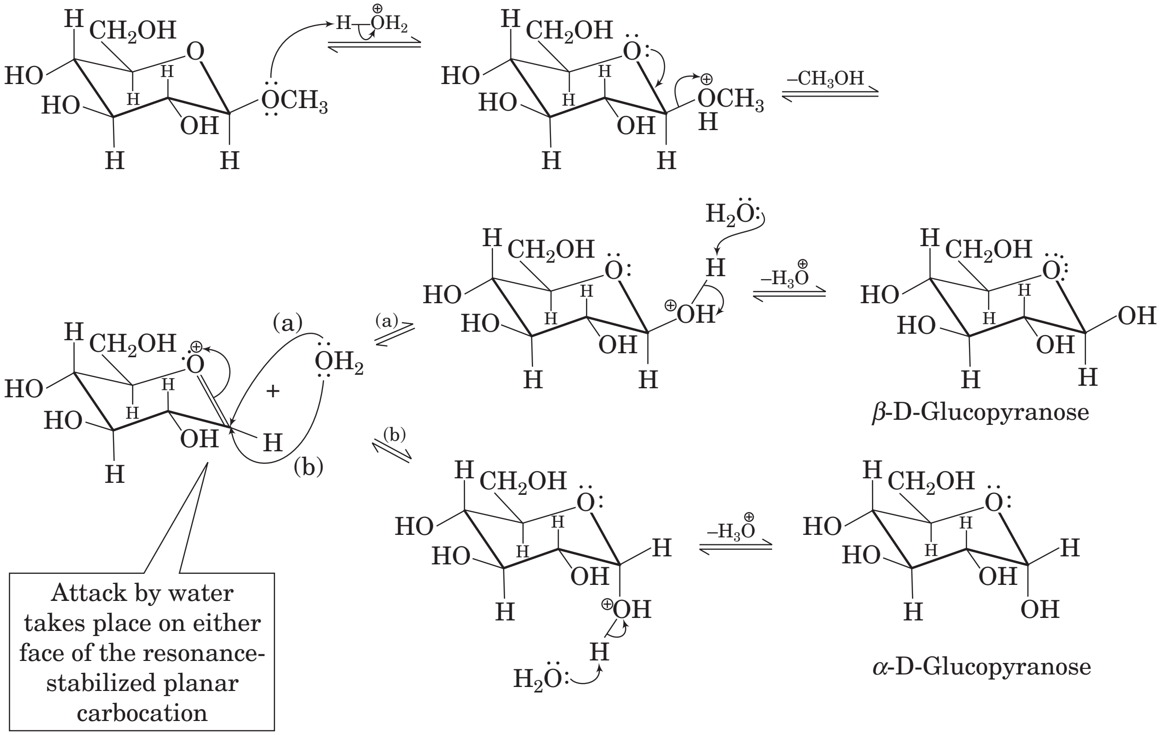
Methyl α-D-glucopyranoside (major product)

The acid protonates the anomeric –OH group. The conjugate acid then eliminates a molecule of water to form a resonance stabilized carbocation which subsequently undergoes nucleophilic attack by methanol. Top face addition followed by loss of a proton produces

β-glycoside, while bottom face addition followed by loss of a proton produces α-glycoside. Surprisingly, D-glucose forms more α-glycoside than β-glycoside. This result is called an *anomeric effect*.

Characteristics of glycosides Since glycosides are acetals, they are stable in basic solutions. In acidic solutions, however, glycosides undergo ready hydrolysis to produce a sugar and an alcohol. For example, when an aqueous solution of methyl β-D-glucopyranoside is made acidic, it undergoes hydrolysis to yield D-glucose as a mixture of the two pyranose forms (in equilibrium with a very small amount of the open-chain form). Glycosides do not react (reduce) with either Fehling's or Tollen's reagent because they are stable in basic solutions, i.e., they do not undergo hydrolysis to give the open-chain form.

The mechanism for the acid-catalyzed hydrolysis of a glycoside may be outlined as follows:



$H-\overset{\oplus}{O}H_2$
$-CH_3OH$
(a)
(b)
$-H_3\overset{\oplus}{O}$
$-H_3\overset{\oplus}{O}$

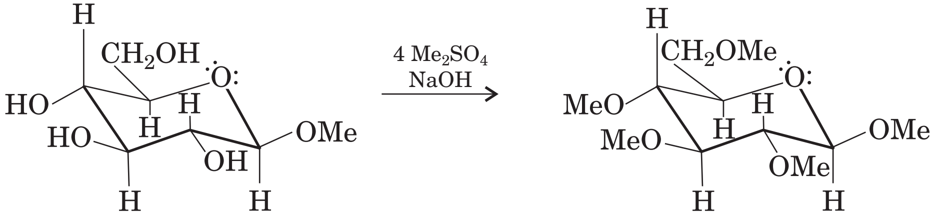
β-D-Glucopyranose

α-D-Glucopyranose

Attack by water takes place on either face of the resonance-stabilized planar carbocation

9.2.13.5 *Formation of Ether (e.g., by Methylation) and Ester (e.g., by Acetylation) Derivatives*

Methylation When methyl D-glucoside is treated with methyl sulphate and sodium hydroxide, the remaining four –OH groups undergo methylation, and as a result, a methyl tetra-*O*-methyl-D-glucoside is obtained:

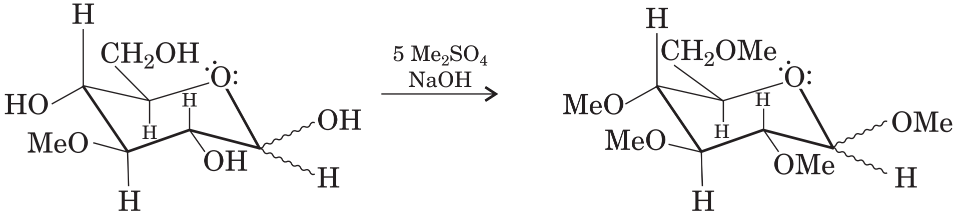


Methyl β-D-glucoside
(Non-reducing sugar)

Methyl β-2,3,4,6-tetra-*O*-methyl-D-glucoside
(Non-reducing sugar)

In this reaction the ether linkages are formed by a modified Williamson synthesis. The Williamson synthesis with most alcohols requires a base stronger than $OH^{\ominus}$ to form the conjugate-base alkoxide. The –OH groups of carbohydrates, however, are more acidic (p*K*a ≈ 12) than those of ordinary alcohols because of the polar effect (–I) of many neighbouring highly electronegative oxygens in the molecule. Consequently, substantial concentration of their conjugate-base alkoxide ions are formed in concentrated NaOH. A large excess of the alkylating agent is to be used because hydroxide itself, present in large excess, also react with the alkylating agent.

Methyl β-2,3,4,6-tetra-*O*-methyl-D-glucoside may also be prepared from D-glucose by allowing it to react with Me_2SO_4/NaOH. However, in that case base-catalyzed epimerization does not take place despite the strongly basic conditions used and this is because the alkylation of the anomeric –OH group is much faster than epimerization. Once this oxygen is alkylated, epimerization can no longer occur.

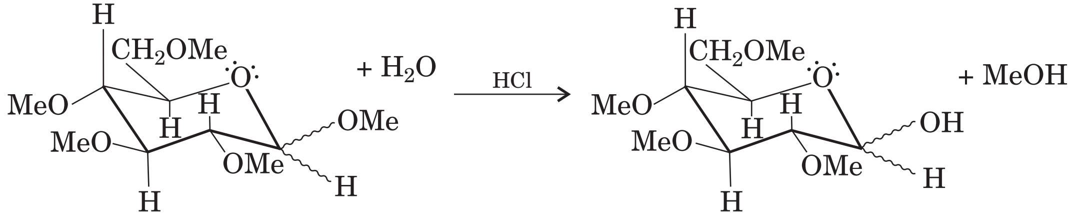


D-Glucopyranose

Methyl 2,3,4,6-tetra-*O*-methyl-D-glucopyranoside

Other reagents used to form methyl ethers of carbohydrates include CH_3I (methyl iodide)/Ag_2O, and the strongly basic $NaNH_2$ (sodium amide) in liquid ammonia followed by CH_3I.

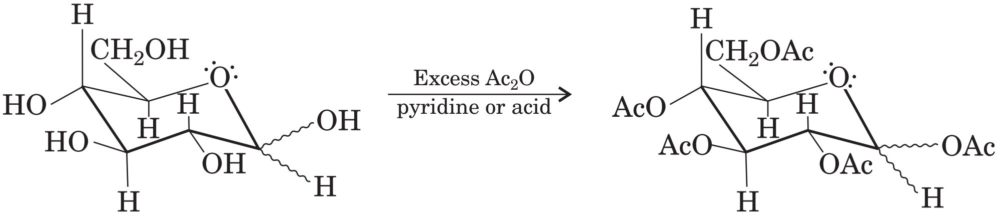
It is to be noted that the alkoxy group at the anomeric carbon is different from the other alkoxy groups in an alkylated carbohydrate molecule because it is part of the glycosidic linkage. Because it is an acetal, it can be hydrolyzed easily in aqueous acid under mild conditions. The other alkoxy groups are ordinary ethers and do not hydrolyze under these conditions. They require much stronger conditions for hydrolytic cleavage.



Methyl 2,3,4,6- tetra-*O*-methyl-D-glucopyranoside (Non-reducing sugar)

2,3,4,6- Tetra-*O*-methyl-D-glucopyranoside (Reducing sugar)

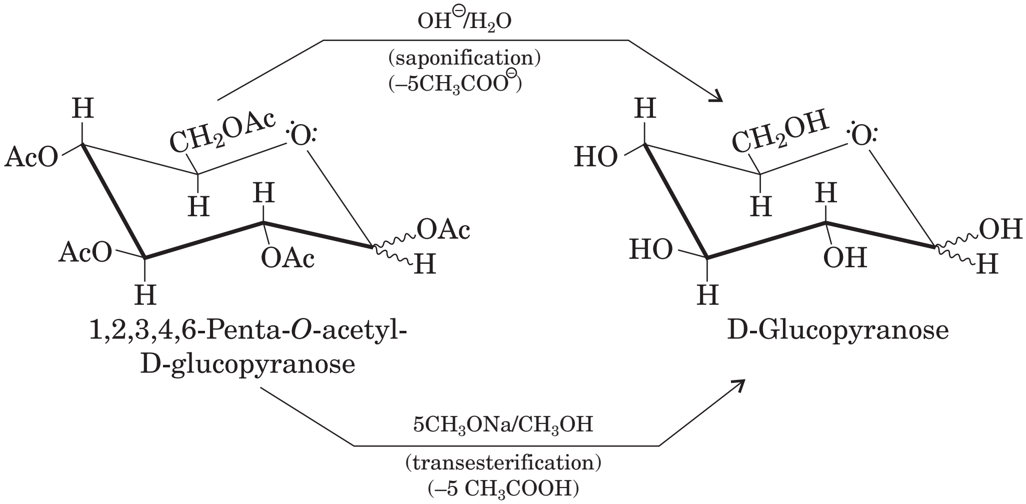
Acetylation The hydroxyl groups of carbohydrates, like those of other alcohols, can be esterified. For example, when D-glucose is treated with excess acetic anhydride in the presence of pyridine or acid, 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose in obtained.



D-Glucopyranose

1,2,3,4,6-Penta-*O*-acetyl-D-glucopyranose (83%)

Carbohydrate esters can be saponified in base or the —COR group can be removed by transesterification with an alkoxide such as methoxide:



1,2,3,4,6-Penta-*O*-acetyl-D-glucopyranose

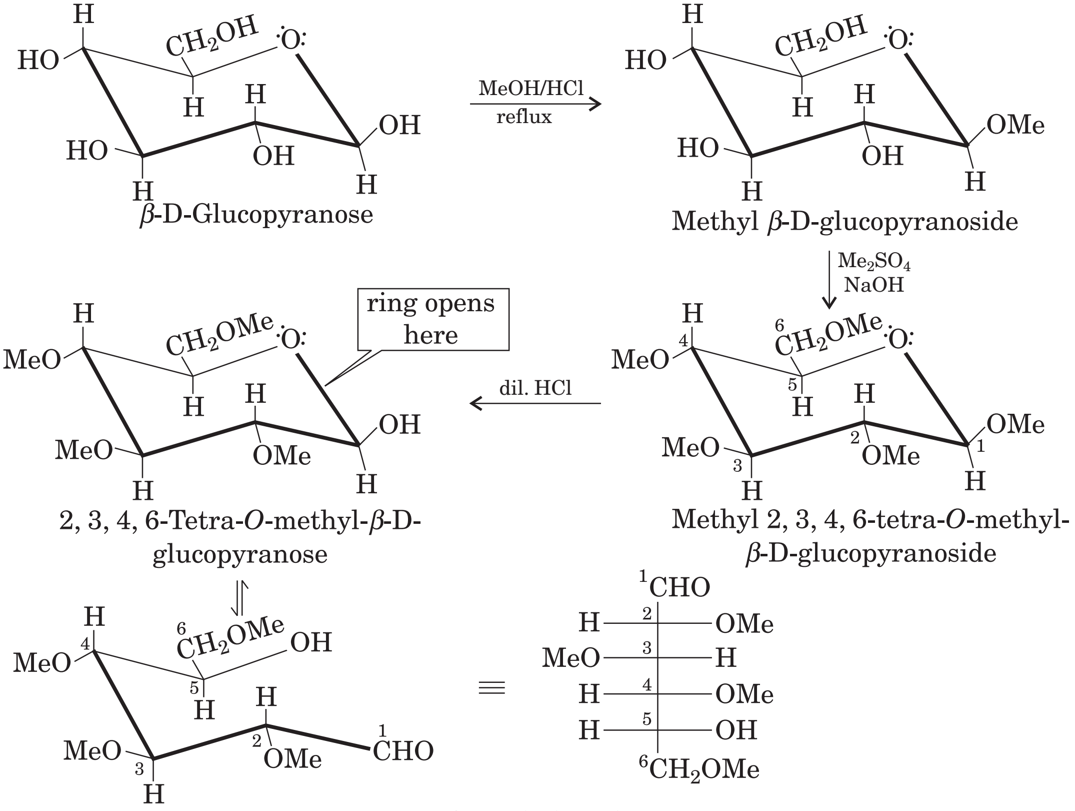
D-Glucopyranose

Ethers as well as esters are used as protecting groups in reactions involving carbohydrates. Ethers and esters also find use in the characterization of carbohydrates by chromatography and mass spectrometry because they have broader solubility characteristics and greater volatility than carbohydrates themselves.

9.2.13.6 Determination of Ring Size

1. Haworth and Hirst by the classical oxidative degradation reaction were able to prove that the naturally occurring D-(+)-glucose possesses a six-membered pyran-like ring structure. The method of determining ring size is as follows:

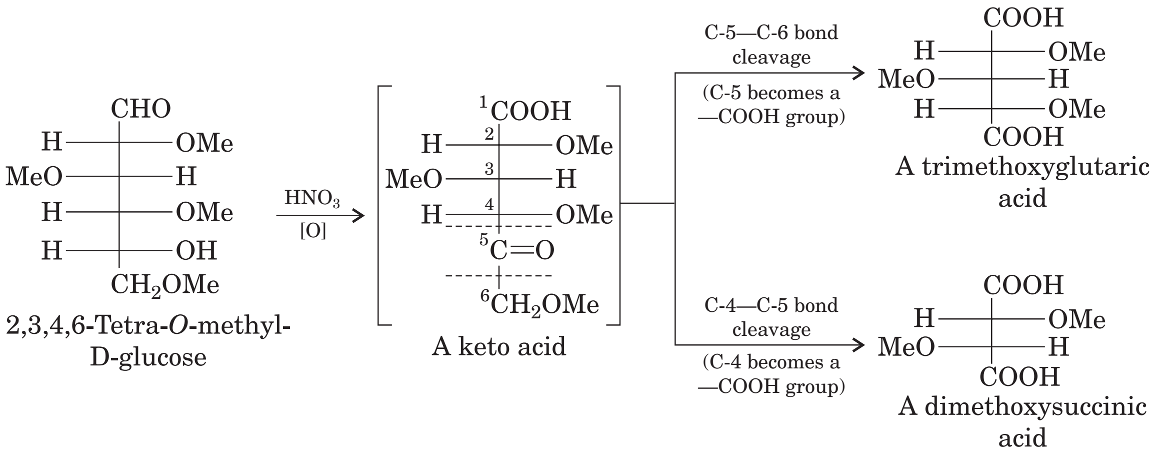
Methyl *β*-D-glucopyranoside, obtained by refluxing *β*-D-glucose with methanol in the presence of hydrogen chloride, is treated with dimethyl sulphate (Me_2SO_4) in aqueous NaOH to yield methyl 2,3,4,6-tetra-*O*-methyl-*β*-D-glucopyranoside. Being an acetal methyl glycoside does not undergo isomerization or fragmentation in basic media. When this compound is hydrolyzed by dilute hydrochloric acid, 2,3,4,6-tetra-*O*-methyl-D-glucopyranose is obtained. The resulting compound is a cyclic hemiacetal which, in solution, remains in equilibrium with a little open-chain aldehyde form (the other four —OCH_3 groups are ordinary ether groups and therefore, they remain unaffected under this reaction conditions).


β-D-Glucopyranose
MeOH/HCl
reflux
Methyl β-D-glucopyranoside
Me2SO4
NaOH
Methyl 2, 3, 4, 6-tetra-O-methyl-β-D-glucopyranoside
dil. HCl
ring opens here
2, 3, 4, 6-Tetra-O-methyl-β-D-glucopyranose
≡

2, 3, 4, 6-Tetra-*O*-methyl-D-glucose
(open-chain form)

The open-chain structure of tetra-*O*-methyl-D-glucose contains an aldehyde group, four methoxy (—OCH_3) groups, and a free, unmethylated –OH group. This –OH group is actually located on the carbon atom which participates in the hemiacetal ring formation. If the six-membered ring is correct, this –OH group would be located on C-5. Determination of ring size now becomes a matter of finding out which carbon bears the free –OH group.

When 2,3,4,6-tetra-*O*-methyl-D-glucose was vigorously oxidized by nitric acid, the —CHO group is converted into a —COOH group and the —CHOH-group is converted into a keto group. Under such conditions, the intermediate keto acid undergoes C—C bond cleavage yielding carboxylic acids containing lesser number of carbon atoms. The bond fission may take place on either side of the $>C{=}O$ group. In actual practice, a trimethoxyglutaric acid and a dimethoxy succinic acid are isolated as the product of oxidation. A mixture of five-carbon and four-carbon acids could be formed only by cleavage on either side of C-5.

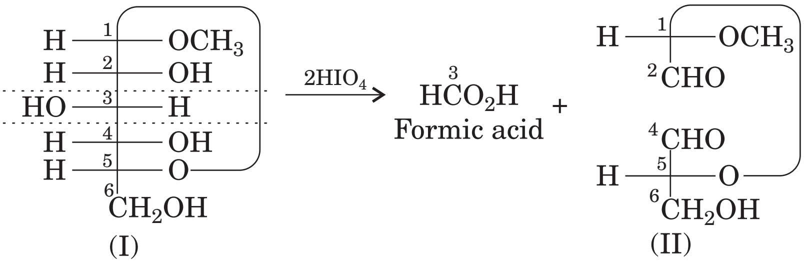

2,3,4,6-Tetra-O-methyl-D-glucose
HNO₃ [O]
A keto acid
C-5—C-6 bond cleavage
(C-5 becomes a —COOH group)
A trimethoxyglutaric acid
C-4—C-5 bond cleavage
(C-4 becomes a —COOH group)
A dimethoxysuccinic acid

Therefore, it must be C-5 that carries the carbonyl oxygen of the intermediate keto acid, C-5 that carries the free –OH group in the tetra-*O*-methyl-D-glucose, C-5 that is involved in formation of acetal ring of the original glucoside. Therefore, methyl *β*-D glucoside and necessarily *β*-D-glucose must contain a six-membered ring.

[It is to be noted that this conclusion is based on the assumption that no change in ring position takes place during methylation of glucose.]

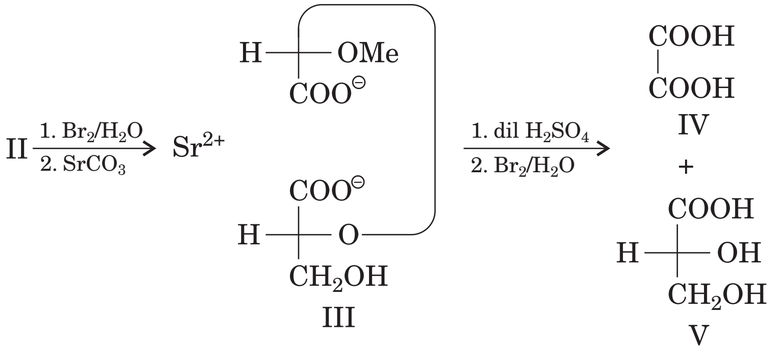
2. Periodic acid oxidation method for ring size determination

Hudson (1937) oxidized methyl *α*-D-glucoside (I) with periodic acid and found that two moles of periodic acid were consumed; 1 mole of formic acid and one mole of a dialdehyde (II) were produced.

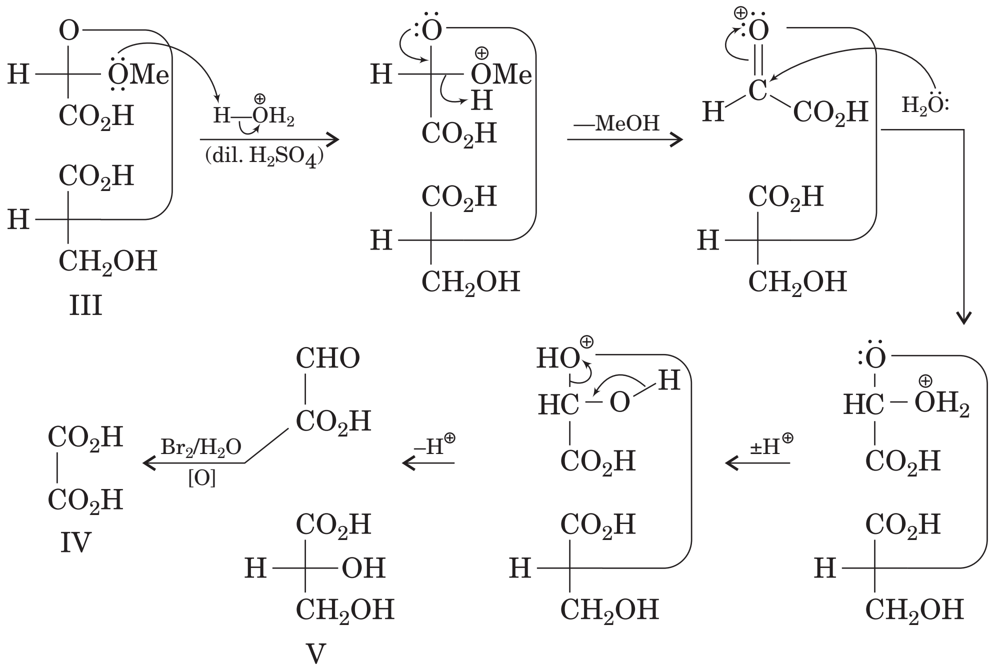


The dialdehyde (II) may further be cleaved to smaller fragments by a series of reactions and then from these a clear idea of ring size is obtained. In fact, this is a continuation of Hudson's oxidation.

(II) on oxidation with bromine-water in the presence of strontium carbonate, gave the crystalline salt (III). (III) on acidification with sulphuric acid (for hydrolysis), followed by further oxidation with bromine-water produces oxalic acid (IV) and D-(–)-glyceric acid (V). Isolation of (III), (IV), and (V) indicates that the ring in (I) is δ-(i.e., a pyranose ring); this is also supported by the fact that one C-atom is eliminated as formic acid, and that two molecules of periodic acid were consumed.



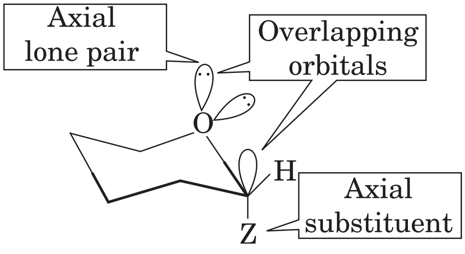
Mechanism for the step 2:



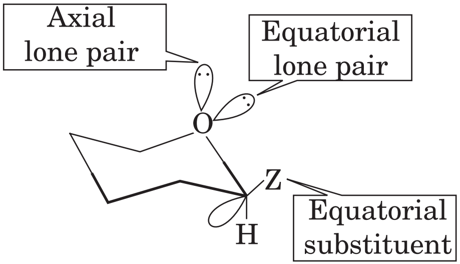
9.2.13.7 *The Anomeric Effect*

The preference for the axial position by an electronegative substituent such as alkoxy (—OR) or acyloxy (—OCOR) group bonded to the anomeric carbon is called the *anomeric effect*. When D-(+)-glucose, for example, is allowed to react with methanol in the presence of HCl to form a glucoside, the major product is methyl α-D-glucopyranoside (with the —OMe group on C-1 axial) and the minor product is methyl β-D-glucopyranoside (with the —OMe group on C-1 equatorial). This observation indicates that the α-glucoside is thermodynamically more stable than the β-glucoside, even though conformationally the β-anomer (with all equatorial substituents) is expected to be more stable. The stability of the α-glucoside may be explained as follows. If the substituent —OMe is axial, one of the ring oxygen's lone pair is in an orbital that is parallel to the σ^* antibonding orbital of the C—O bond.

The molecule then can be stabilized by electron delocalization–some of the electron density moves from the sp^3 orbital of oxygen into the σ^* antibonding orbital. When the —OMe group is in equatorial position, neither of the orbitals that contain a lone pair is aligned correctly for overlap.

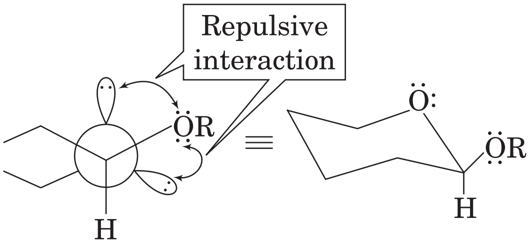


Z=OMe or OCOMe



Z=OMe or OCOMe

The preference of the substituent for the axial position is also due to the destabilization of β-glucoside caused by the dipole-dipole or electron pair-electron pair repulsion (rabbit ear effect). This can be shown as follows:



9.2.14 Chemistry of D-(–)-Fructose (Fruit Sugar)

Naturally occurring ketohexoses are, in fact, very rare and most important member of this class of compounds is D-(–)-fructose. It occurs widely in fruits and combined with glucose, in the disaccharide sucrose (common table sugar). Fructose, which is the sweetest of the common sugars, accounts for the intense sweetness of honey. Since the naturally occurring D-fructose is laevorotatory, it is also called *laevulose*.

9.2.14.1 Preparation of D-(–)-Fructose

Fructose can be prepared from cane-sugar, i.e., sucrose and inuline as follows:

1. When sucrose (cane-sugar) is heated with dilute sulphuric acid, it undergoes hydrolysis to yield an quimolar mixture of D-(–)-fructose and D-(+)-glucose from which fructose is separated by fractional crystallization.

$$\underset{\substack{\text{Sucrose}\\\text{(a disaccharide)}}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow[\Delta]{H_2SO_4} \underset{\text{D-(+)-Glucose}}{C_6H_{12}O_6} + \underset{\text{D-(–)-Fructose}}{C_6H_{12}O_6}$$

2. Fructose is prepared commercially by the acidic hydrolysis of inuline, a polysaccharide made of fructose molecules.

$$\underset{\text{Inuline}}{(C_6H_{10}O_5)_n} + nH_2O \xrightarrow[\substack{\text{or } H_2SO_4\\\Delta}]{HCl} \underset{\text{Fructose}}{nC_6H_{12}O_6}$$

9.2.14.2 Properties of D-(–)-Fructose

D-(–)-Fructose is a white crystalline solid having m.p. 102°C. It is soluble in water but insoluble in ether. It is sparingly soluble in ethanol. It reduces Fehling's solution and Tollens' reagent. With excess of phenylhydrazine it forms an osazone. The chemical reactions of fructose are, in fact, similar to those of glucose, any differences being due to the fact that the former is a ketone and the latter is an aldehyde. The most noticeable difference is the behaviour towards oxidizing agents. Fructose is not oxidized by bromine-water or an alkaline solution of iodine. When oxidized with nitric acid it gives a mixture of acids, each containing less than six carbon atoms.

9.2.14.3 Structure of D-(–)-Fructose

1. Elucidation of open-chain ketohexose structure

The structure of fructose has been derived form a consideration of the following facts and conclusions therefrom:

(i) Elemental analysis and molecular weight determination confirm that the molecular formula of D-(–)-fructose is $C_6H_{12}O_6$.

(ii) When treated with acetic anhydride, fructose forms a pentacetate derivative. This reaction, therefore, shows that there are five –OH groups in a molecule of fructose. Since fructose is a stable molecules, the five –OH groups must be attached with five different carbon atoms.

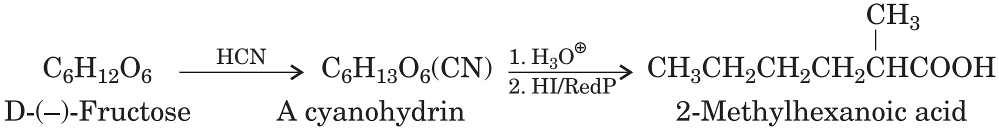
(iii) Fructose forms monoxime with hydroxylamine. Therefore, it contains a carbonyl group $\left(\rangle C{=}O \text{ or } {—}CHO\right)$.

(iv) Fructose cannot be oxidized by mild oxidizing agent like bromine-water. This indicates that the carbonyl group is not aldehydic but ketonic $\left(\gt C{=}O\right)$. Again, when oxidized with HNO_3, fructose is converted into a mixture of trihydroxyglutaric, tartaric, and glycolic acids. Since a mixture of carboxylic acids each containing lesser number of carbon atoms than fructose is obtained, the carbonyl group in fructose must present as a ketonic group.

(v) Fructose can be reduced by sodium and ethanol to a mixture of two epimeric hexa hydric alcohols, namely, sorbitol and mannitol. These on further reduction with hydroiodic acid and red phosphorus at 100°C, a mixture of 2-iodohexane and *n*-hexane is obtained. The formation of the latter two compounds indicates that the six carbon atoms in fructose molecule form a consecutive, unbranched chain.

$$\underset{\text{(–)-Fructose}}{C_6H_2O_6} \xrightarrow{\text{Na/EtOH}} \underset{\substack{\text{Sorbitol and}\\ \text{mannitol}}}{C_6H_{14}O_6} \xrightarrow{\text{RedP/HI}} \underset{n\text{-Hexane}}{C_6H_{14}}$$

(vi) Fructose adds one molecule of HCN to give a cyanohydrin which on hydrolysis followed by reduction with hydroiodic acid and red phosphorus yields 2-methylhexanoic acid.



$$\underset{\text{D-(–)-Fructose}}{C_6H_{12}O_6} \xrightarrow{\text{HCN}} \underset{\text{A cyanohydrin}}{C_6H_{13}O_6(CN)} \xrightarrow[\text{2. HI/RedP}]{\text{1. }H_3O^{\oplus}} \underset{\text{2-Methylhexanoic acid}}{CH_3CH_2CH_2CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}HCOOH}$$

The formation of a C-2 branched carboxylic acid indicates that the ketonic group is adjacent to one of the terminal carbon atoms (C-2 position).

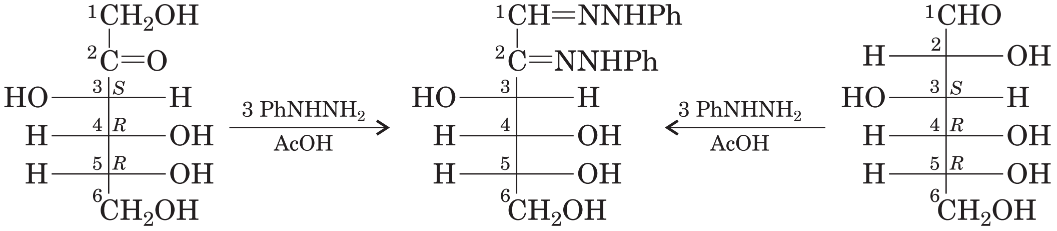
On the basis of the above experimental facts the structure for (–)-fructose may be written as follows:

$$HO\overset{1}{C}H_2\overset{2}{C}O\overset{3}{C}HOH\overset{4}{C}HOH\overset{5}{C}HOH\overset{6}{C}H_2OH$$

The open-chain structure of (–)-fructose has three chiral centres (C-3, C-4 and C-5), and therefore, it can have $2^3 = 8$ stereoisomers, which differ in configurations at these chiral centres. Natural (–)-fructose is one of them.

2. Elucidation of the configuration of (–)-fructose

(–)-Fructose reacts with excess of phenylhydrazine to form an osazone which is found to be identical with glucosazone. Since osazone formation involves only the C-1 and C-2 of glucose, therefore, the configurations of the chiral centres C-3, C-4 and C-5 in fructose is identical to that in glucose. Hence, (–)-fructose has configuration I, i.e., (–)-fructose is (3*S*, 4*R*, 5*R*)-1,3,4,5,6-pentahydroxy-2-hexanone:



(I)
D-(–)-Fructose

Same osazone
(Glucosazone or fructosazone)

D-(+)-Glucose

3. Ring structure of D-(–)-fructose

Although most of the reactions of D-(–)-fructose can be explained on the basis of the open chain structure(I), the following facts remain unexplained:

(i) D-(–)-Fructose is unable to form an addition product with sodium bisulphate

(ii) There are two types of D-(–)-fructose, designated as *α*-D-(–)-fructose and *β*-D-(–)-fructose.

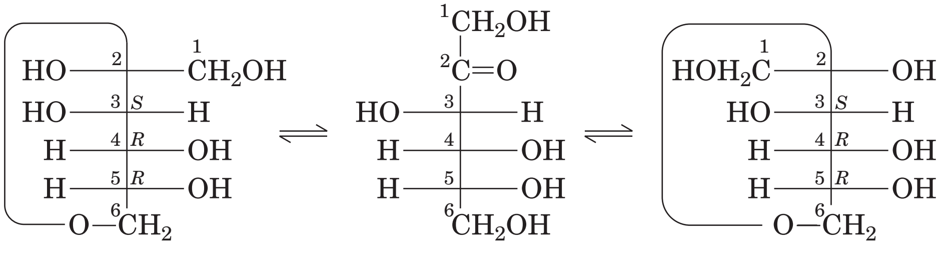
(iii) In aqueous solution the two types of D-(–)-fructose undergo mutarotition.

(iv) Only one molecule of methanol reacts with one molecule of D-(–)-fructose in the presence of anhydrous HCl to yield two fructosides, namely methyl *α*-D-(–)-fructoside and methyl *β*-D-(–)-fructoside. These have properties resembling those of a full acetal.

(v) (–)-Fructose does not show appreciable carbonyl absorption in its infrared spectrum.

(vi) Fructose pentaacetate does not react with NH_2OH.

To account for these facts, a cyclic hemiacetal structure has been proposed for D-(–)-fructose in which the $>C{=}O$ group is not free rather it forms a hemiacetal with the –OH group situated at C-6. Formation of hemiacetal generates a new chiral centre at C-2 and that is why two anomeric D-(–)-fructose are possible.



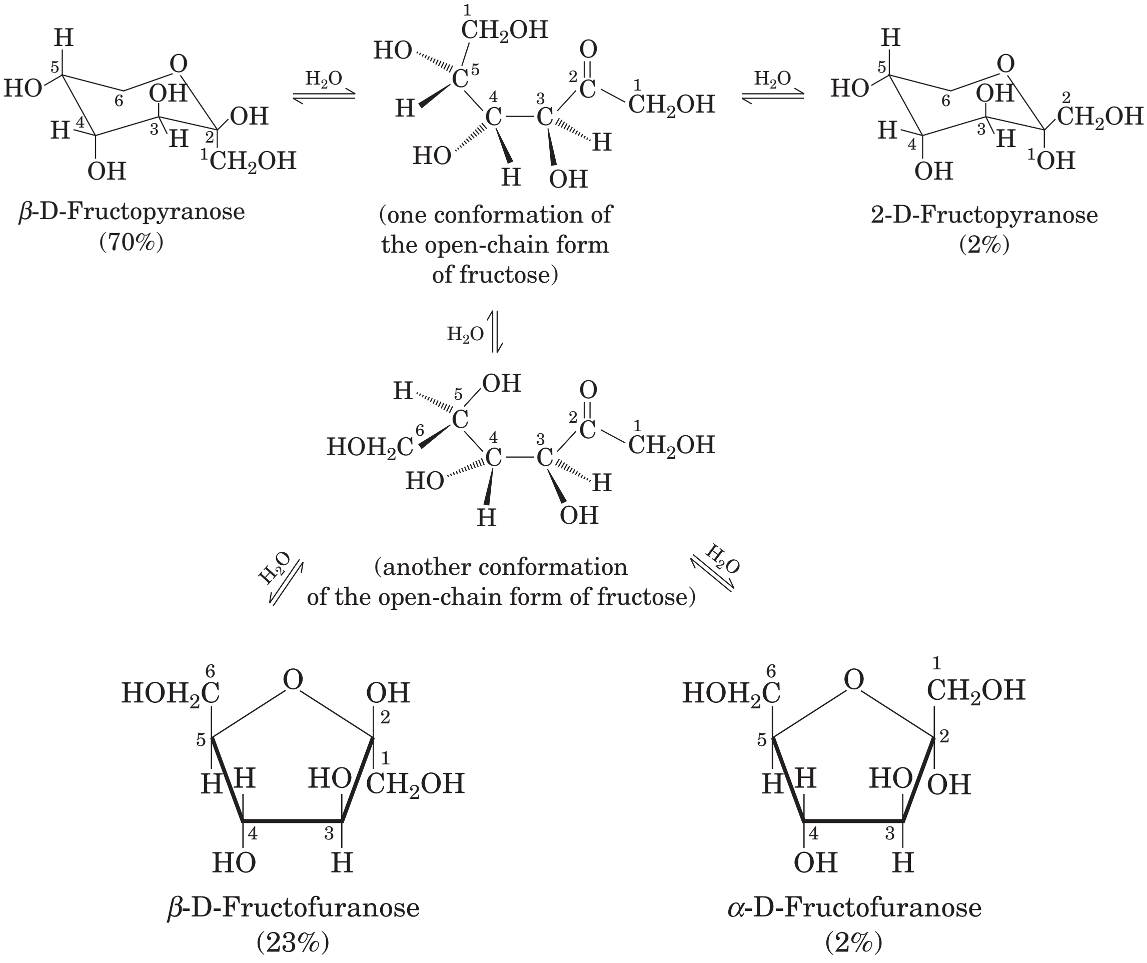
β-D-(–)-Fructopyranose
mp. 103°C; $[\alpha]_D = -133°$

Open-chain
form of D-fructose

α-D-(–)-Fructopyranose

Mutarotation of fructose

The only crystalline form of fructose that is isolated is *β*-D-fructopyranose, which has an initial specific rotation of –133.5° and undergoes rapid mutarotation to –92°. This mutarotation involves not only isomerization between the *α*- and *β*-pyranose forms, but also conversion to the furanose forms. The fructofuranose structure is important because furanose is present in sucrose and other oligosaccharides in that form.



β-D-Fructopyranose (70%)

(one conformation of the open-chain form of fructose)

2-D-Fructopyranose (2%)

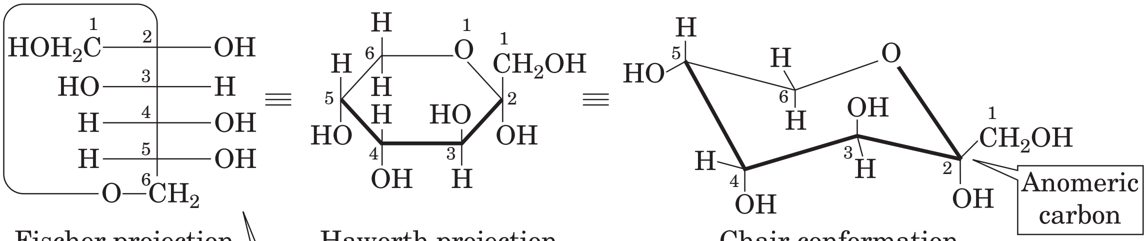
(another conformation of the open-chain form of fructose)

β-D-Fructofuranose (23%)

α-D-Fructofuranose (2%)

Conversion of the Fischer projection of *α*-D-(–)-fructopyranose and *β*-D-(–)-fructopyranose into their chair conformations through Haworth projection Since D-fructopyranoses are laevorotatory, the oxide ring is Fischer projections is drawn to the left.

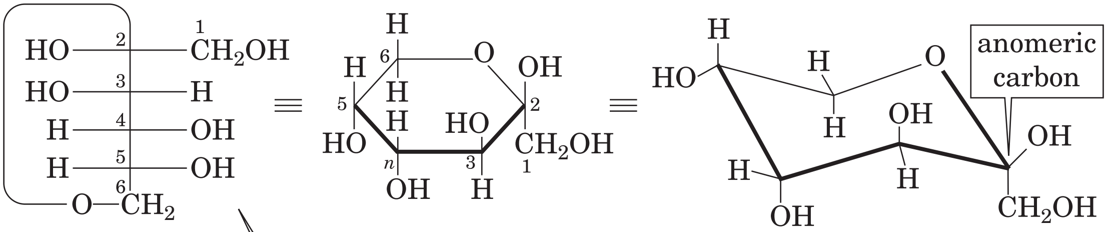
(i) α-D-(–)-Fructopyranose:



Fischer projection Haworth projection Chair conformation

It is the α-anomer because the hemiacetal —OH and the —OH at the reference carbon (i.e., C-5) are on the same side in the Fischer projection

(ii) β-D-(–)-Fructopyranose:



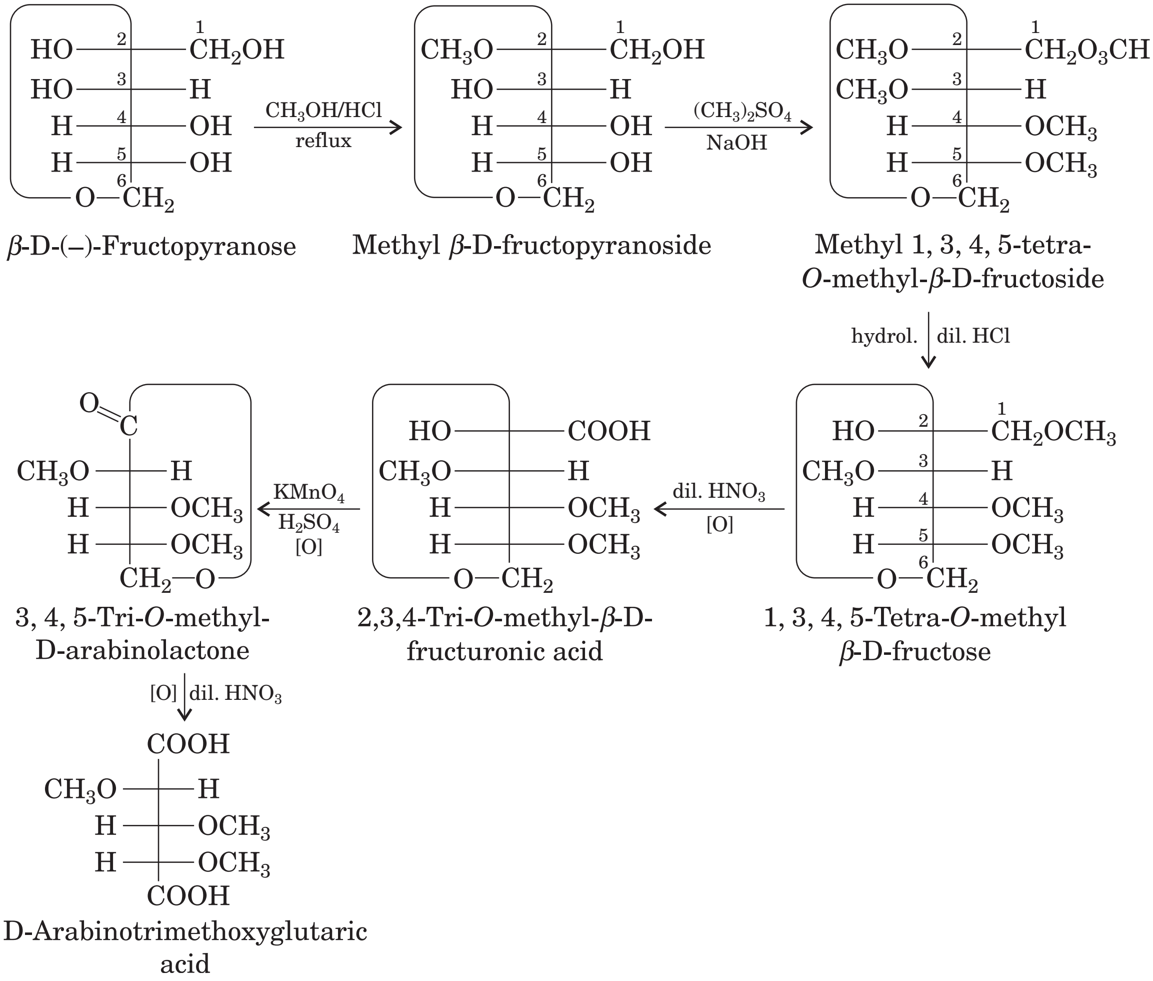
Fischer projection Haworth projection Chair conformation

It is the β-anomer because the hemiacetal —OH and the —OH at the reference carbon (i.e., C-5) are on different sides in the Fischer projection

β-D-(–)-Fructopyranose is relatively more stable than the α-anomer. This is because in the former two less bulky –OH groups (C-2 and C-5) are attached to axial bonds, whereas in the latter a less bulky –OH group along with a more bulky —CH_2OH group are attached to axial bonds.

Determination of ring size

The presence of pyranose ring structure of D-(–)-fructose has been confirmed from the following degradation studies when D-arabinotrimethoxyglutaric acid has been isolated.


β-D-(–)-Fructopyranose
CH3OH/HCl reflux
Methyl β-D-fructopyranoside
(CH3)2SO4 NaOH
Methyl 1, 3, 4, 5-tetra-O-methyl-β-D-fructoside
hydrol. dil. HCl
1, 3, 4, 5-Tetra-O-methyl β-D-fructose
dil. HNO3 [O]
2,3,4-Tri-O-methyl-β-D-fructuronic acid
KMnO4 H2SO4 [O]
3, 4, 5-Tri-O-methyl-D-arabinolactone
[O] dil. HNO3
D-Arabinotrimethoxyglutaric acid

The pyranose structure has been confirmed by X-ray analysis of crystalline β-D-(–)-fructopyranose.

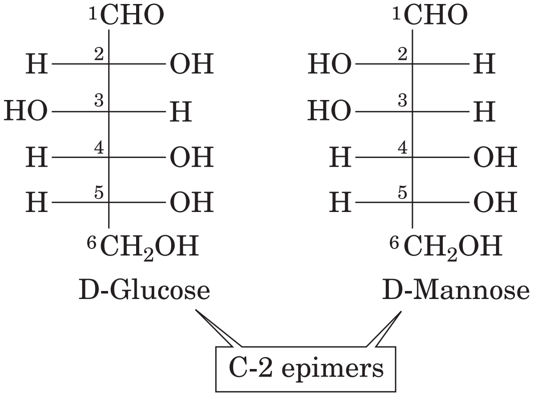
SOLVED PROBLEMS

1. **Write down the name of the simplest known keto sugar and mention the stereochemical point of its difference from the simplest known aldosugar.**

Solution Dihydroxyacetone ($HOCH_2COCH_2OH$) is the simplest known ketosugar. It has no chirality centre, whereas the simplest known aldosugar glyceraldehyde ($OHC\overset{*}{C}HO$-HCH_2OH) has one chirality centre and it exists as two enantiomeric forms.

2. Define the term epimer and illustrate with an example.

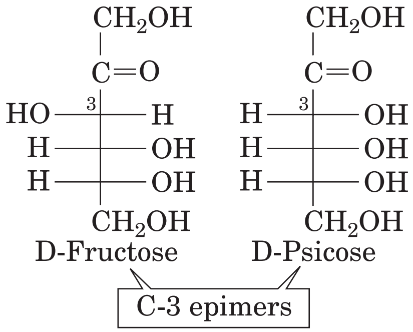
Solution Diastereoisomers that differ in configuration at only one chirality centre are called epimers. D-glucose and D-mannose are C-2 epimers because they differ in configuration only at C-2.



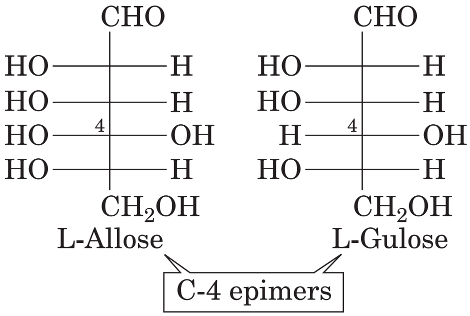
3. Write down the names and Fischer projection of (i) C-3 epimer of D-fructose, (ii) C-4 epimer of L-allose, (iii) C-5-epimer of L-altose, and (iv) C-3 epimer of D-talose.

Solution

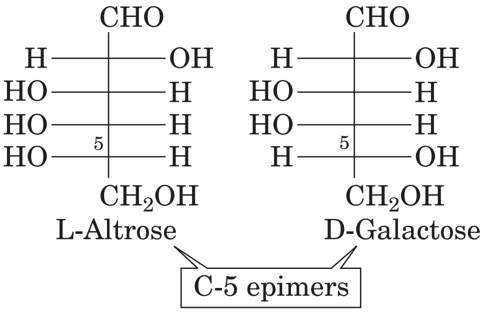
(i)



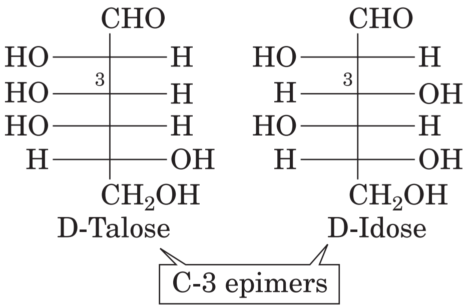
(ii)



(iii)

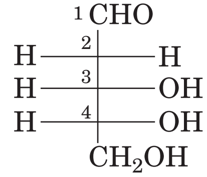


(iv)



4. What do you mean by deoxy sugars? Give an example.

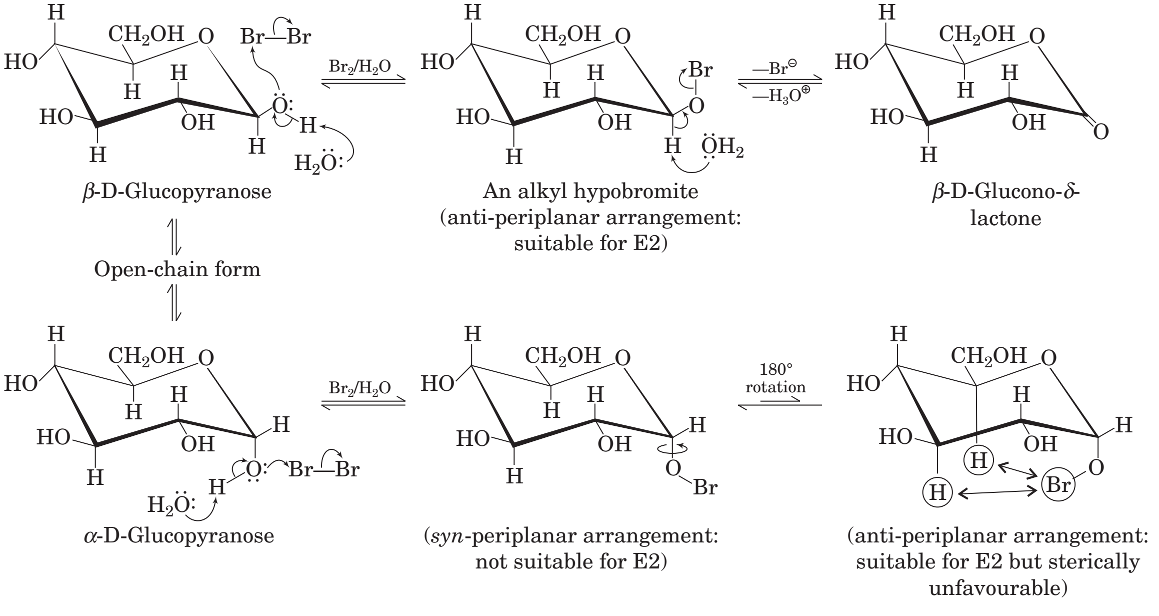
Solution In some naturally occurring sugars, there is a hydrogen atom in place of one or more of the –OH groups. These are called deoxy sugars. For example:



2-Dexy–D-ribose

5. *β*-D-Glucopyranose undergoes oxidation by bromine-water 250 times as fast as that of *α*-D-glucopyranose. Explain.

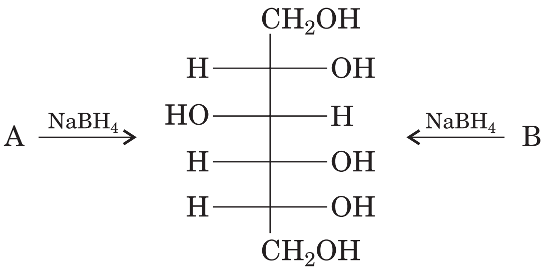
Solution The mechanism of bromine-water oxidation of a D-glucopyranose involves formation of an alkyl hypobromite followed by loss of HBr. The C—H and O—Br bonds are antiparallel to each other. This is in agreement with the stereoelectronic requirement of an E2 reaction. The *β*-anomer can achieve this stereochemistry easily. Also, the elimination of a proton from the axial position is more favourable than an equatorial position. So, it undergoes ready oxidation by bromine-water. In the *α*-anomer, on the other hand, the axial hydrogens at C-3 and C-5 hinder an anti-periplanar arrangement of the C—H and C—Br bonds and in fact, it takes up a stable syn-periplanar conformation from which elimination of HBr, i.e., dehydrobromination, does not take place. The very slow rate of the oxidation of the *α*-anomer is due to its conversion into the *β*-anomer (through the open-chain form) followed by its oxidation.


Br₂/H₂O
—Br⊖
—H₃O⊕
β-D-Glucopyranose
An alkyl hypobromite (anti-periplanar arrangement: suitable for E2)
β-D-Glucono-δ-lactone
Open-chain form
Br₂/H₂O
180° rotation
α-D-Glucopyranose
(syn-periplanar arrangement: not suitable for E2)
(anti-periplanar arrangement: suitable for E2 but sterically unfavourable)
CH₂OH
HO
OH
H
O
Br—Br
H₂Ö:
OH₂
Br

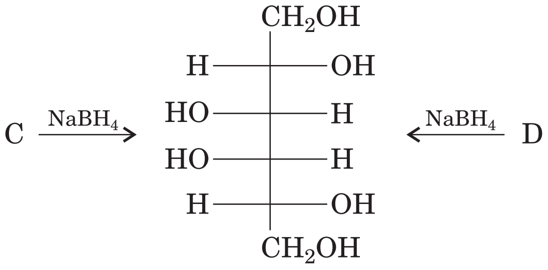
6. Bromine water is a better reagent than Tollens' reagent for the oxidation of aldoses to aldonic acids—why?

Solution Tollens reagent is strongly basic and for this, it promotes epimerization and enediol rearrangement of the aldose. However, bromine-water being acidic does not cause epimerization or rearrangment of the aldose. For this reason, bromine-water is a better reagent than Tollens' reagent for the oxidation of aldoses to aldonic acids.

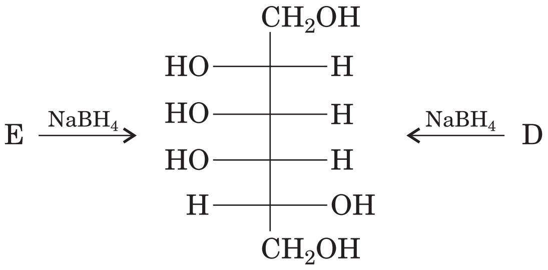
7. Identify the aldohexoses A—F:

(i) 

An alditol

(ii) 

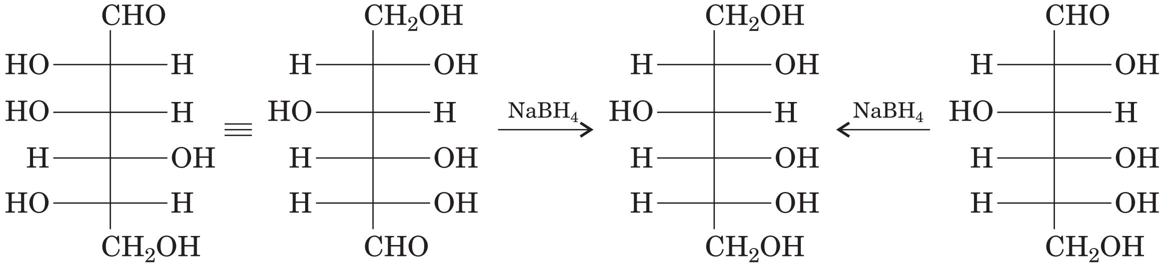
An alditol

(iii) 

An alditol

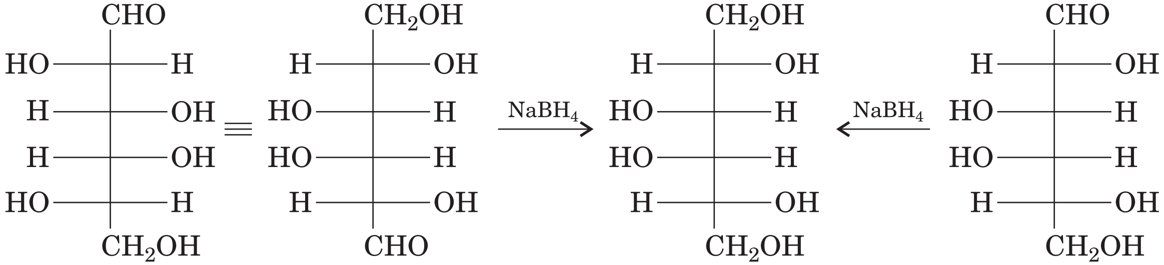
Solution

(i) L-gulose and D-glucose can be reduced by $NaBH_4$ to give the same alditol. Therefore, (A) is L-gulose and (B) is D-glucose.



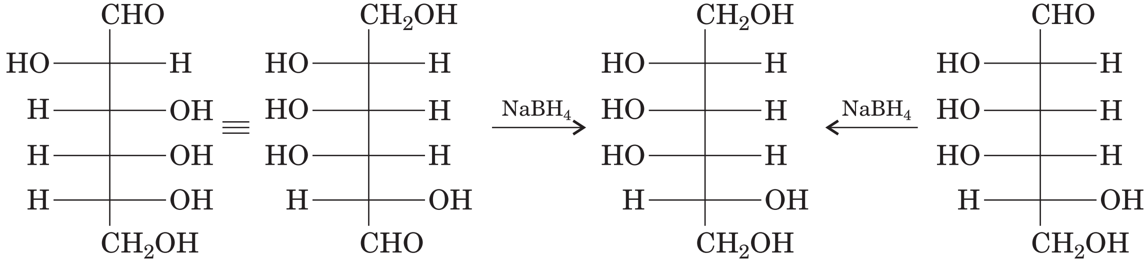
L-Gulose (A) — L-Gulose (drawn upside down) — An alditol — D-Glucose (B)

(ii) L-galactose and D-galactose (two enantiomers) can be reduced by $NaBH_4$ to yield the same alditol. Therefore, (c) is L-galactose and (D) is D-galactose.



L-Galactose (C) — L-Galactose (drawn upside down) — An alditol — D-Galactose (D)

(iii) D-Altrose and D-talose on sodium borohydride reduction produce the same alditol. Therefore, (E) is D-altrose and (F) is D-talose.

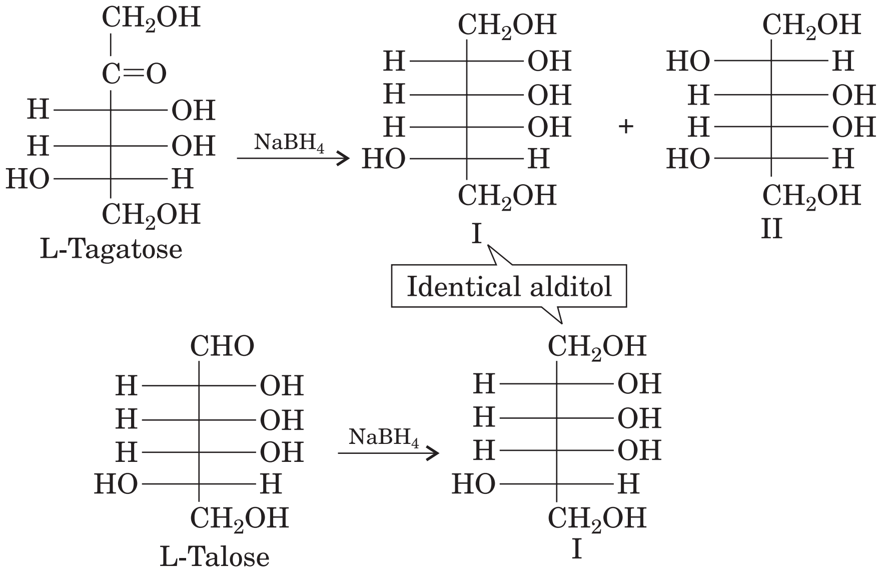


D-Altrose (E) — D-Altrose (drawn upside down) — An alditol — D-Talose (F)

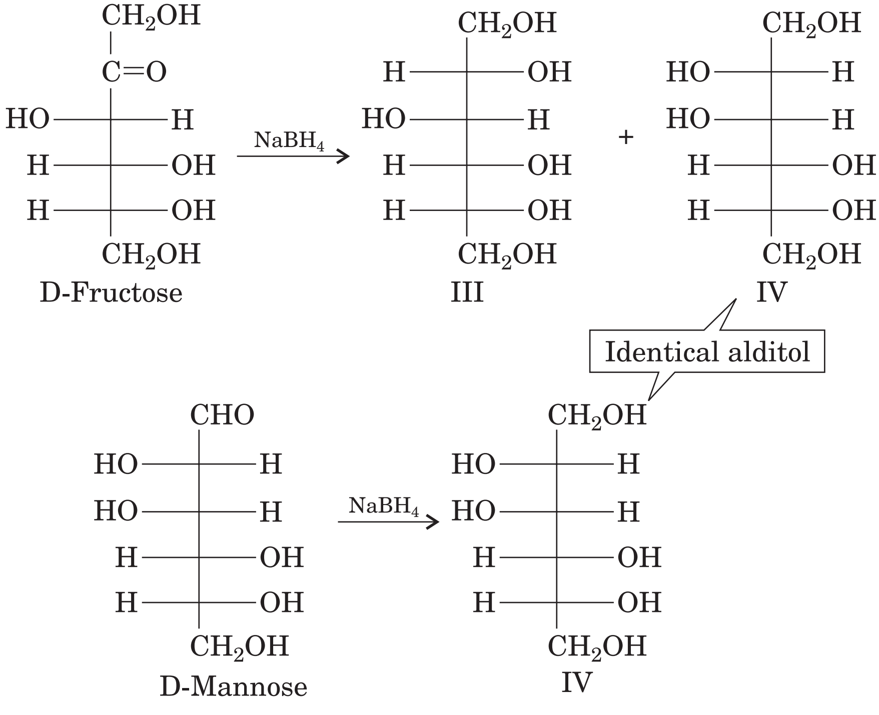
8. Identify the ketohexose which on $NaBH_4$ reduction produces two epimeric alditols, one of which may also be obtained on $NaBH_4$ reduction of: (a) L-talose (b) D-mannose and (c) L-altrose.

Solution

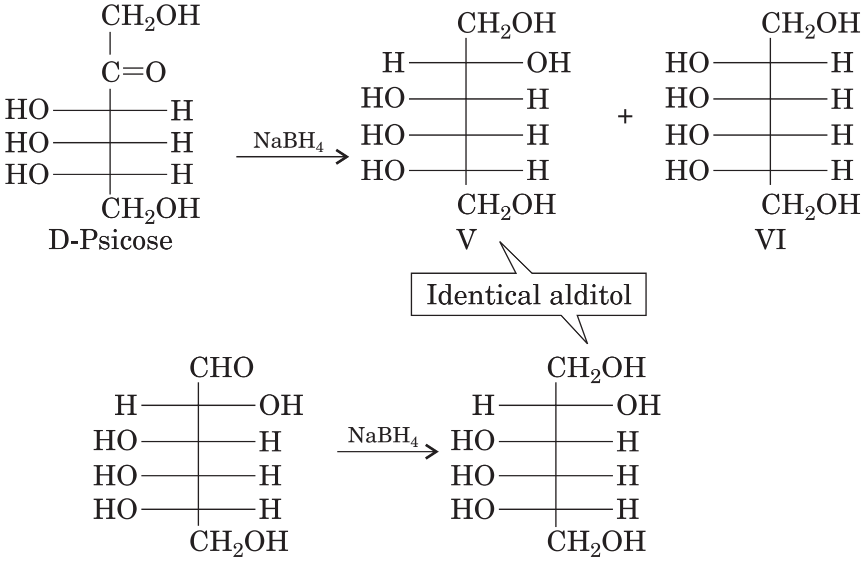
(a) L-Tagatose can be reduced to give two alditols one of which may also be obtained on reduction of L-talose.



(b) D-Fructose can be reduced to two alditols, one of which may also be obtained on reduction of D-mannose.



(c) L-Psicose can be reducd with $NaBH_4$ to give two alditols, one of which can be obtained on reduction of L-altrose.

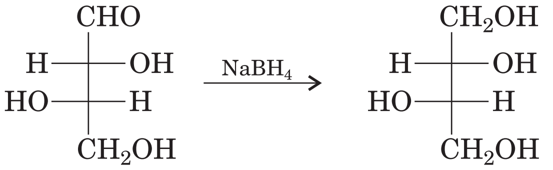


D-Psicose V VI

L-Altrose V

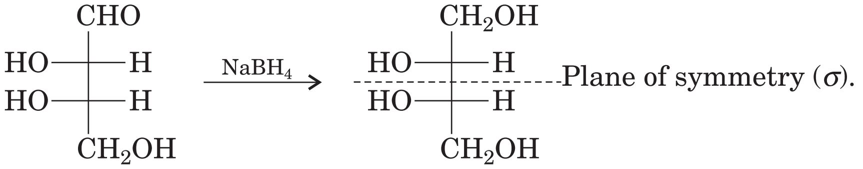
9. How would you distinguish between L-(+)-erythrose and L-(+)-threose by the polarimetric analysis of their $NaBH_4$ reduction products?

Solution The reduction product of L-(+)-threose is chiral, whereas the reduction product of L-(+)-erythrose in achiral (it has a plane of symmetry). Therefore, the aldotetrose whose reduction product is found to be optically active by polarimetric analysis is L-(+)-threose and the aldotetrose whose reduction product is found to be optically inactive is L-(+)-erythrose.



L-(+)-Threose

An alditol
(optically active)

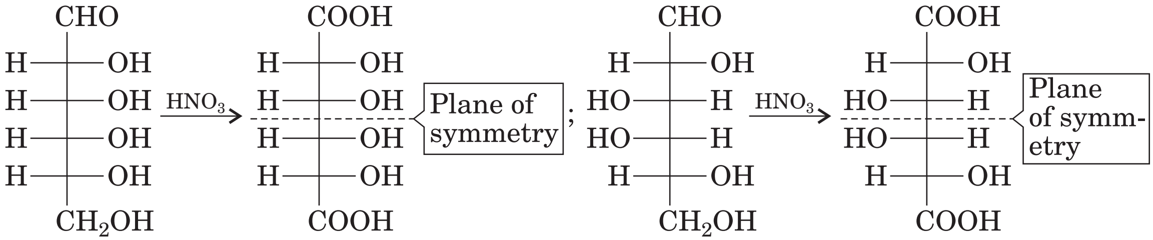


L-(+)-Erythrose

An alditol
(optically inactive)

10. Which two D-aldohexoses on HNO_3 oxidation produce *meso* aldaric acids?

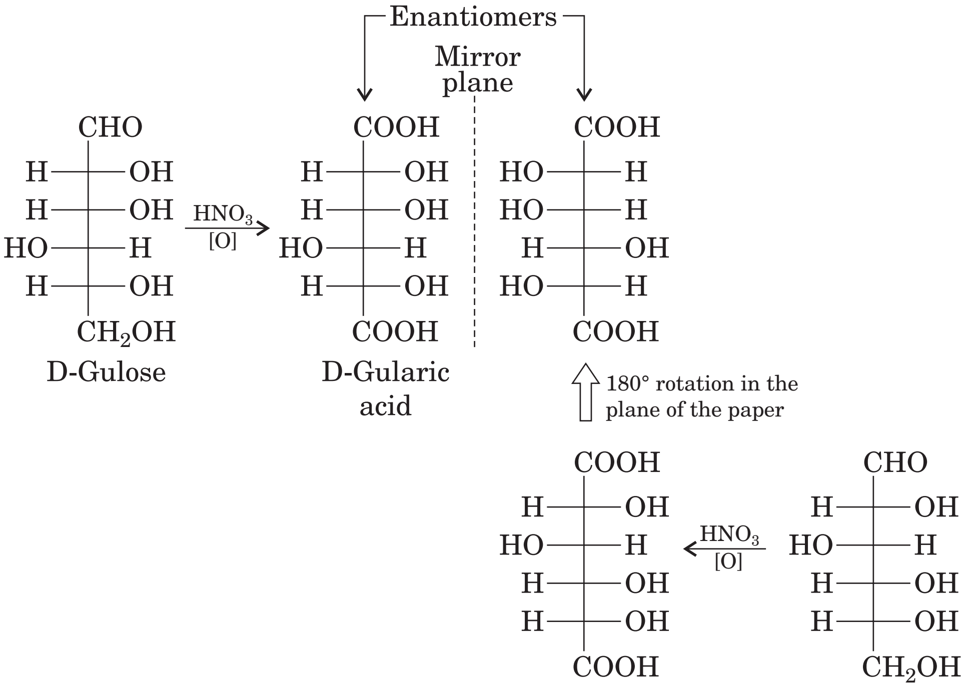
Solution D-Allose and D-galactose are the two D-aldohexoses which on HNO_3 oxidation produce *meso* aldaric acids because in both of them C-2 has mirror image relationship with C-5 and C-3 has mirror image relationship with C-4.



D-Allose D-Allaric acid (a *meso* compound) D-Galactose D-Galactaric acid (a *meso* compound)

11. Predict the optical activity of 1:1 mixture of the aldaric acids obtained on HNO_3 oxidation of D-gulose and D-glucose.

Solution The aldaric acids obtained from D-gulose and D-glucose are, in fact, enantiomers of each other. Therefore, when those two aldaric acids are mixed in 1:1 molar ratio, a mixture is obtained which is optically inactive.

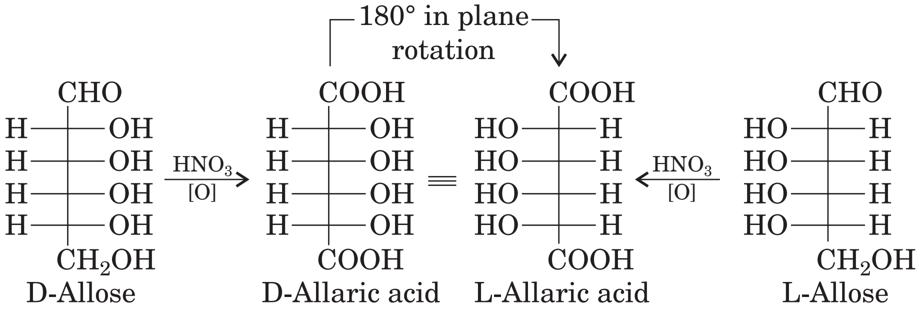


D-Gulose D-Gularic acid D-Glucaric acid D-Glucose

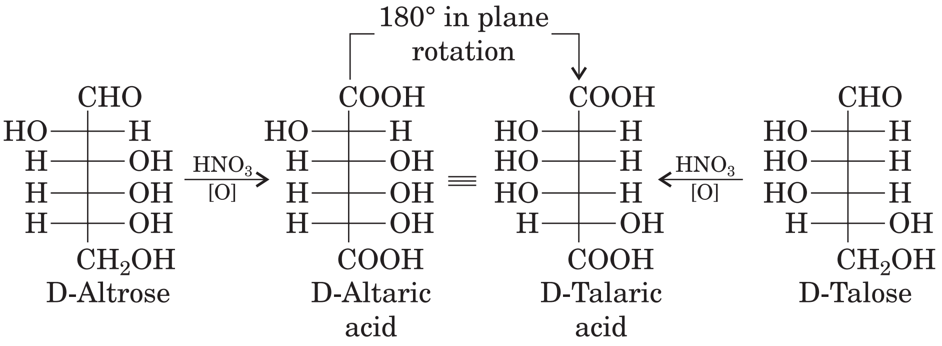
12. Draw the Fischer projections for the five pairs of enantiomeric or diasterisomeric aldohexoses that on HNO_3 oxidation produce identical aldaric acids.

Solution

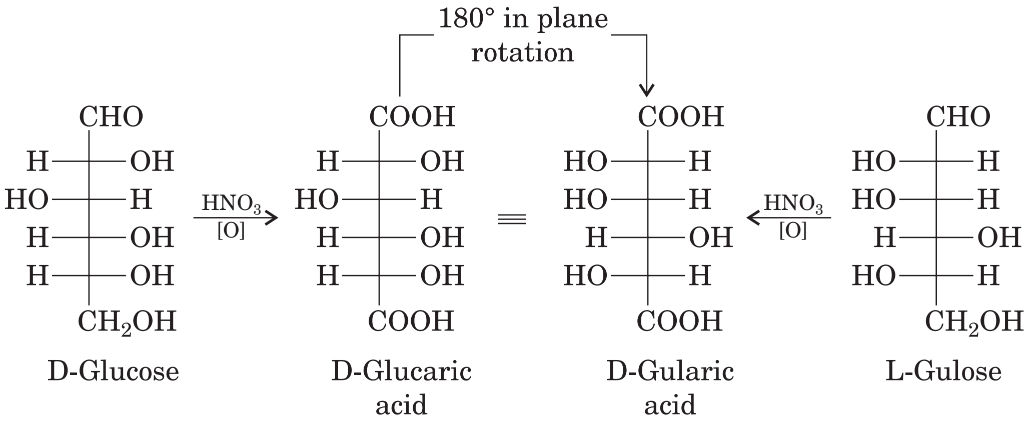
(i) D-Allose and L-allose on oxidation produce the same aldaric acid.



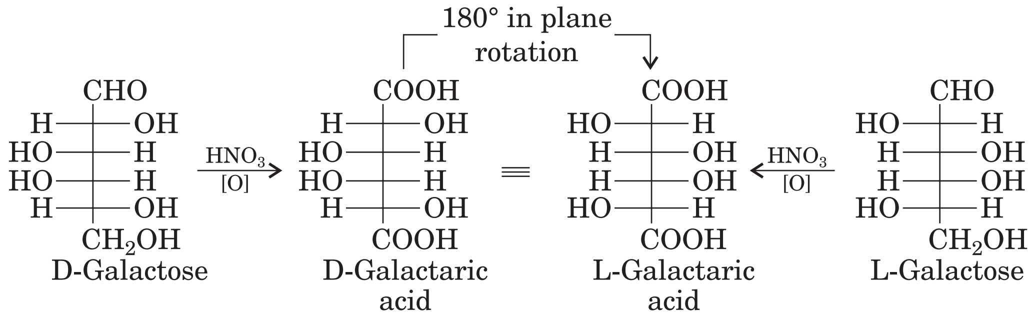
(ii) D-Altrose and D-talose on oxidation produce the identical aldaric acid.



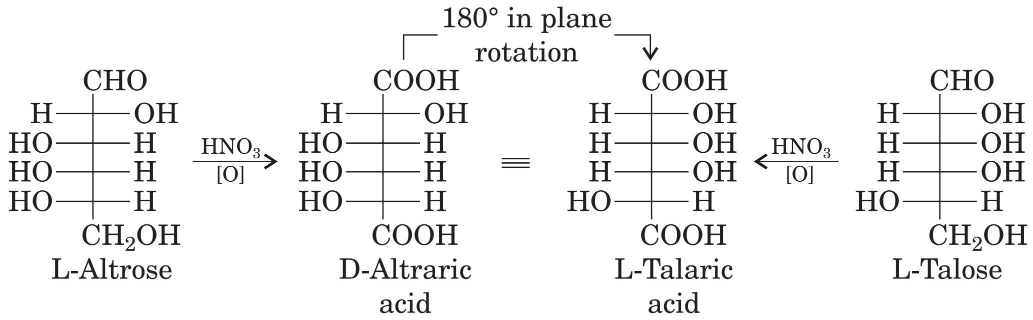
(iii) D-Glucose and D-gulose on oxidation produce the same aldaric acid.



(iv) D-Galactose and L-galactose undergo HNO_3 oxidation to yield the identical aldaric acid.

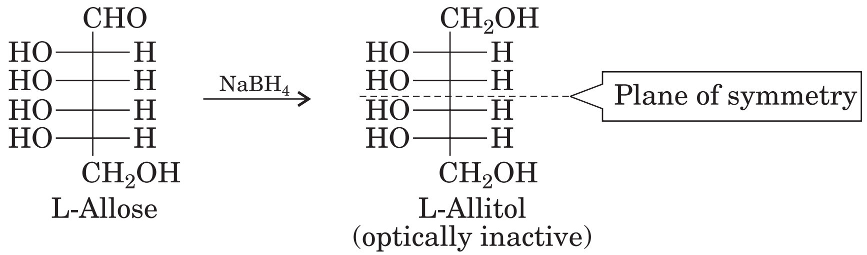


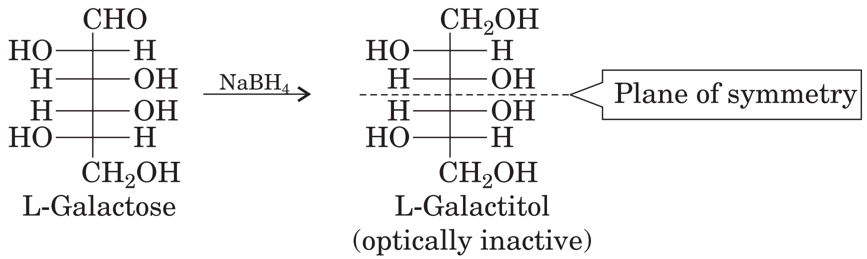
(v) L-Altrose and L-talose on HNO_3 oxidation produce the same aldaric acid.



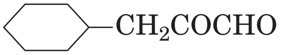
13. Write Fischer projections for all of the L-aldohexoses that would yield optically inactive alditols.

Solution L-Allose and L-galactose undergo $NaBH_4$ reduction to give optically inactive alditols.

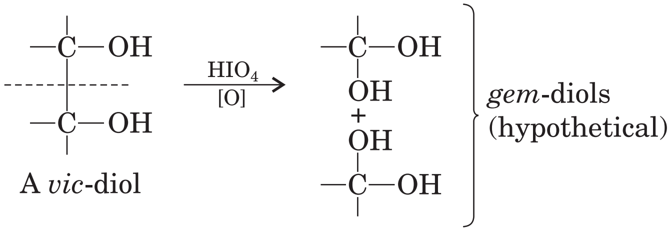




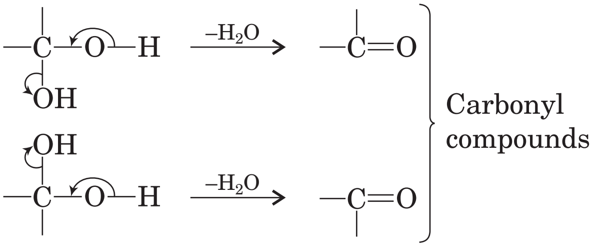
14. Predict the products expected to be formed when each of the following compounds undergo complete oxidative cleavage on treatment with periodic acid (HIO_4). Mention the amount of HIO_4 (in molar equivalent) consumed in each case.

(a) 2,3-Hexanediol (b) 1,2,3-Pentanetriol (c) $C_2H_5COCH(OH)COCH_3$ (d) $CH_3CH_2CHOHCOCH_2OH$ (e) $HOCH_2CHOHCH(OMe)_2$ (f) *cis*-1,2-cyclobutanediol (g) 2,3,4-Trihydroxybutanal (h) 

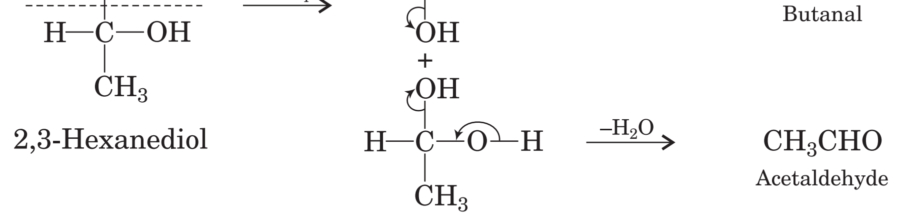
Solution The products expected to be obtained from periodic acid oxidation can be predicted by attaching first one OH group on each carbon atom at the point where C—C bond cleavage is expected to take place.



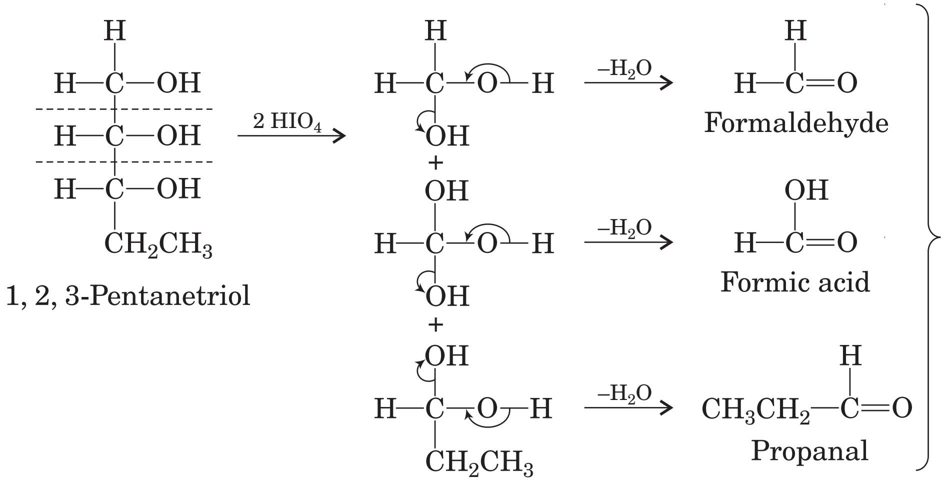
Now, if we recall that *gem*-diols being unstable lose water to form carbonyl compounds, we get the following results:



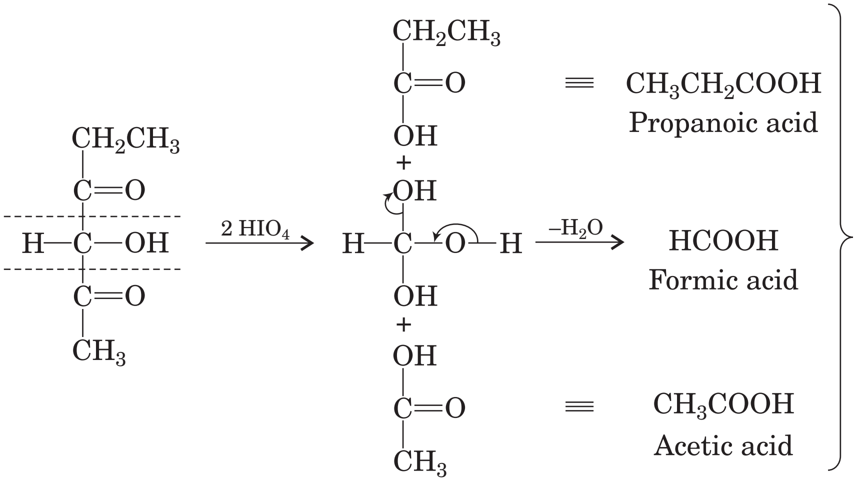
We can then apply this procedure to get the expected products of HIO_4 oxidation of the given compounds. We must not forget that every C—C bond cleavage requires 1 mole of HIO_4.



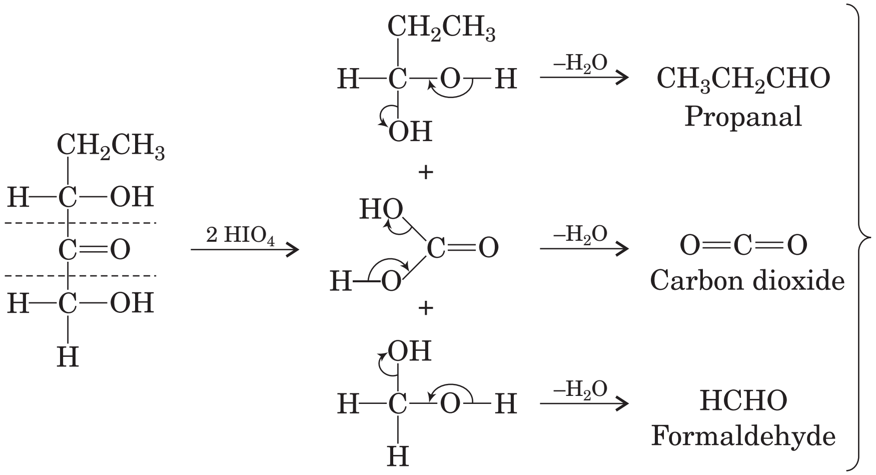
(b)


2 HIO$_4$
–H$_2$O
1, 2, 3-Pentanetriol
Formaldehyde
Formic acid
Propanal

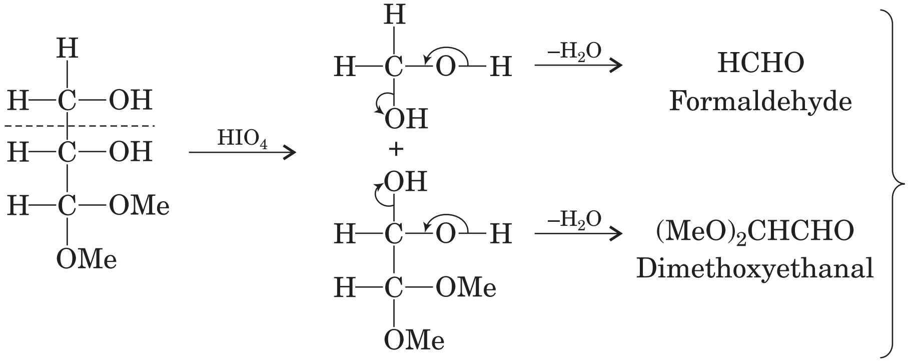
(c)


2 HIO$_4$
–H$_2$O
CH$_3$CH$_2$COOH
Propanoic acid
HCOOH
Formic acid
CH$_3$COOH
Acetic acid

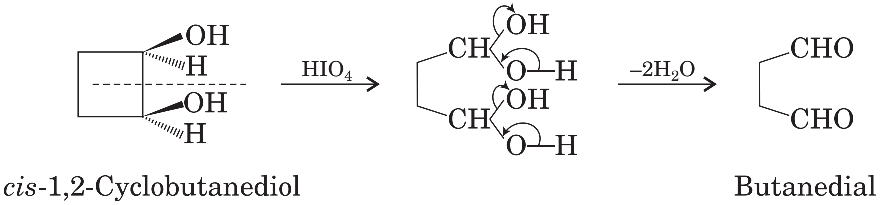
(d)


2 HIO$_4$
–H$_2$O
CH$_3$CH$_2$CHO
Propanal
O=C=O
Carbon dioxide
HCHO
Formaldehyde

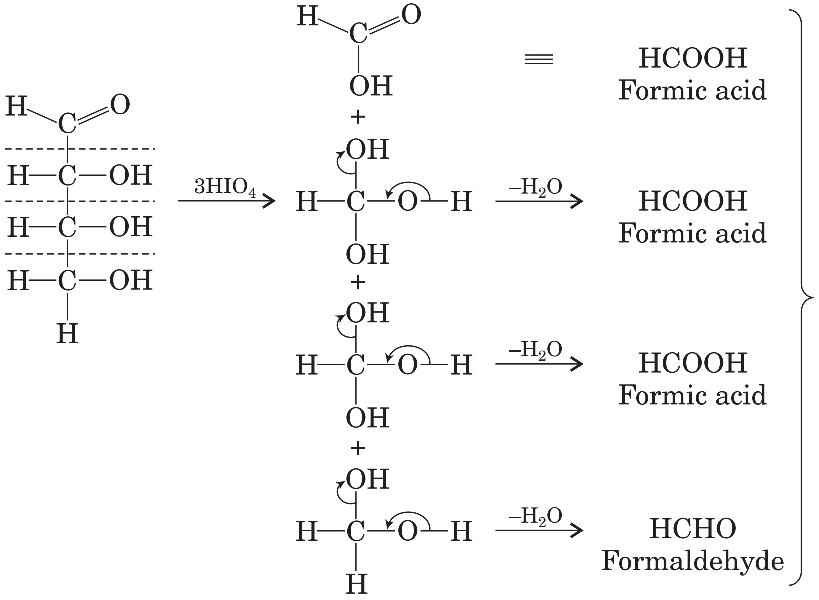
(e)


HIO$_4$
–H$_2$O
HCHO
Formaldehyde
–H$_2$O
(MeO)$_2$CHCHO
Dimethoxyethanal

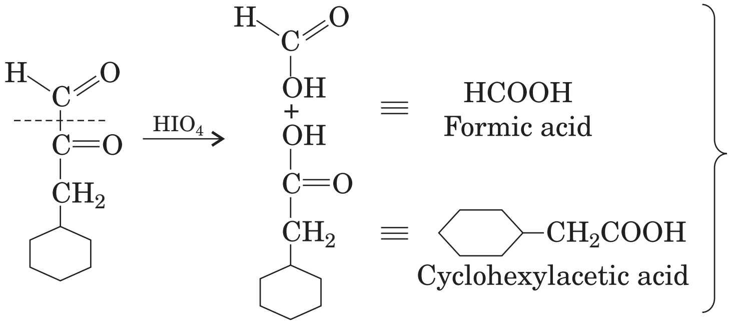
(f)


HIO$_4$
–2H$_2$O
cis-1,2-Cyclobutanediol
Butanedial

(g)


3HIO$_4$
HCOOH
Formic acid
–H$_2$O
HCOOH
Formic acid
–H$_2$O
HCOOH
Formic acid
–H$_2$O
HCHO
Formaldehyde

(h)


HIO$_4$
HCOOH
Formic acid
CH$_2$COOH
Cyclohexylacetic acid

15. (a) Explain why the oxidative cleavage of the 1,2-bond in α-D-glucopyranose by HIO_4 occurs more rapidly than the β-anomer.

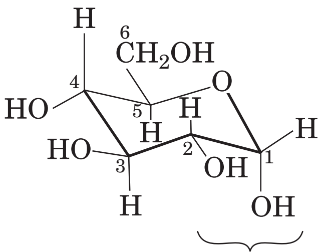
(b) Periodic acid rather than lead tetracetate is used for oxidative cleavage of carbohydrates—Why?

(c) Would you expect α-D-mannopyranose to undergo periodic acid oxidation at a faster rate than β-D-glucopyranose? Give your reasoning.

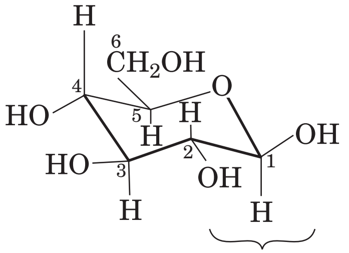
(d) Show how HIO_4 could be used to distinguish between an aldohexose and a ketohexose.

Solution

(a) In α-D-glucopyranose, the two –OH groups at C-1 and C-2 are *cis* to each other, whereas in β-D-glucopyranose they are *trans* to each other. Since a *cis*-1,2-diol can form a cyclic ester with HIO_4 but a *trans*-1,2-diol cannot, the α-anomer undergoes HIO_4 oxidation but the β-anomer does not. In fact, the β-anomer becomes converted into the α-anomer through the open-chain form and then the α-anomer takes part in oxidation. For this, the oxidation of the β-anomer occurs relatively slowly.



a,e : *cis*
D-Glucopyranose
(α-anomer)

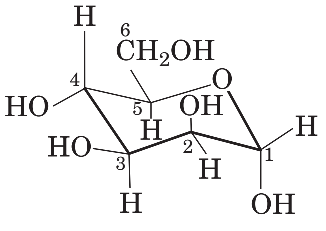


e,e : *trans*
D-Glucopyranose
(β-anomer)

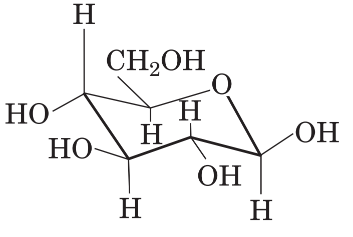
(b) Periodic acid (HIO_4) works well in aqueous medium, whereas lead tetracetate [$Pb(OAc)_4$] gives very good results in organic solvents. Since most simple sugars are highly soluble in water (due to formation of extensive H-bonding), periodic acid rather than lead tetracetate is used for their oxidative cleavage.

(c) α-D-Mannopyranose is expected to undergo HIO_4 oxidation at a faster rate than β-D-glucopyranose.

In the more stable chair conformation of α-D-mannopyranose, the –OH groups at C-2 and C-3 are *cis* to each other, whereas in the more stable chair form of β-D-gluco-pyranose, no two adjacent –OH groups are *cis* to each other.



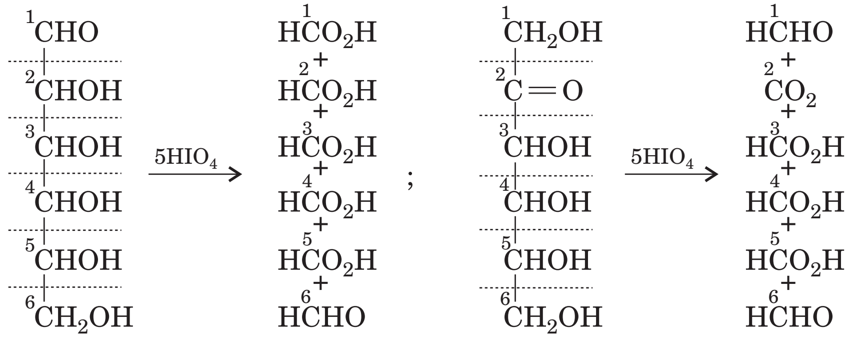
α-D-Mannopyranose
(C-2 and C-3 –OH groups are *cis*)



β-D-Glucopyranose
(no two –OH groups are *cis*)

Since a *cis* 1,2-diol can form a cyclic ester with HIO_4, α-D-mannopyranose undergoes oxidative cleavage of the C-2—C-3 bond readily. β-D-Glucopyranose, on the other hand, becomes converted to the α-anomer through the open-chain form. In the α-anomer, the –OH groups at C-1 and C-2 are *cis* to each other and so it then undergoes oxidative cleavage by HIO_4. Because of following this indirect pathway, the oxidation of β-D-glucopyranose is rather slow.

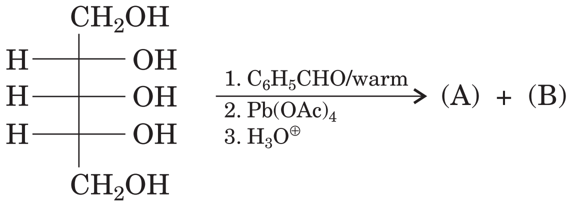
(d) Although oxidative cleavage of an aldohexose and a ketohexose would each require five moles of HIO_4, the results of this oxidation are different. An aldohexose yields five moles of formic acid and one mole of formaldehyde, whereas a ketohexose yields three moles of formic acid, two moles of formaldehyde and one mole of CO_2.



An aldohexose A ketohexose

Therefore, an aldohexose and a ketohexose can be distinguished by measuring the formic acid and formaldehyde formed or simply by identifying gaseous carbon dioxide (which produces a white precipitate of $CaCO_3$ when passed through lime water).

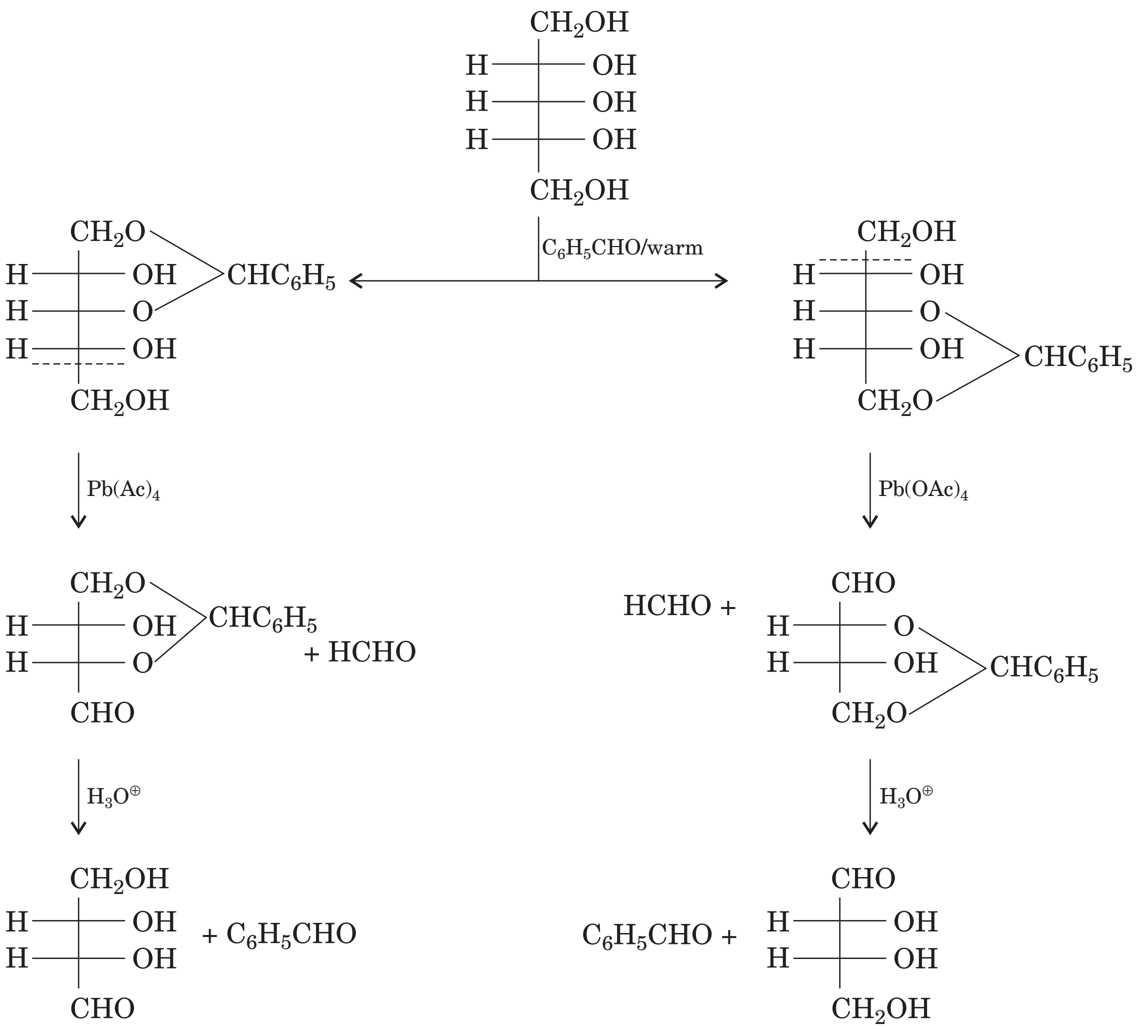
16. (a) Identify (A) and (B) and indicate how they are related to each other.



An alditol

(b) Give the mechanism for the lead tetracetate oxidation of a diol.

Solution It is known that benzaldehyde condenses with *cis*-1,3-diols, lead tetracetate oxidizes 1,2-diols and *O*-benzyledene derivatives can be readily hydrolyzed by acids. Thus, benzaldehyde reacts with the starting alditol to form two diastereoisomeric benzylidine derivatives. One of them leads to the formation of D-erythrose and the other leads to the formation of L-erythrose when treated with lead tetracetate followed by hydrolysis.



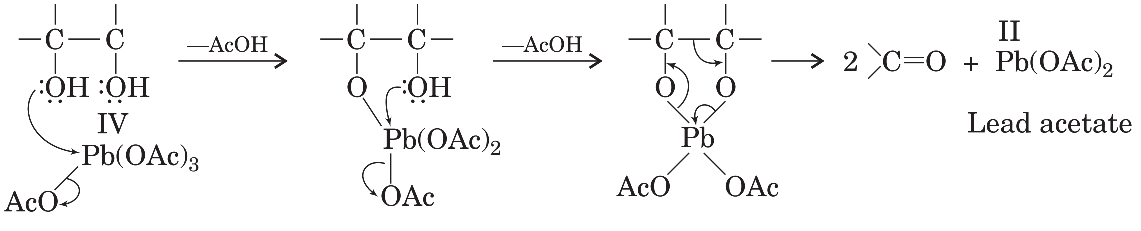
L-Erythrose
(A)

D-Erythrose
(B)

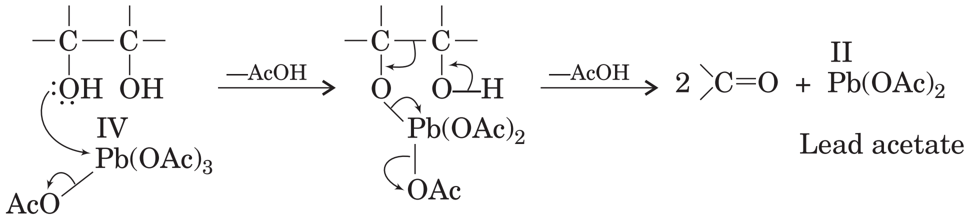
(A) and (B) are two enantiomers.

(b) The mechanistic steps involved in lead tetracetate oxidation of a *vic*-dial may be outlined as follows:

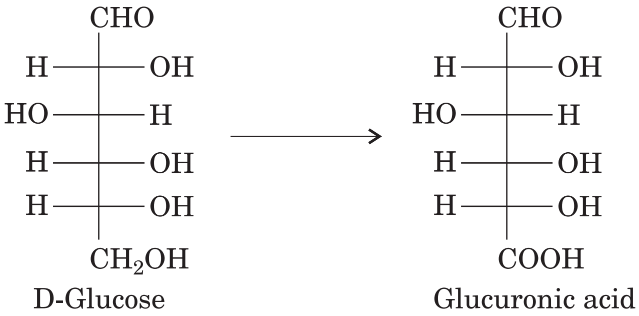
Cyclic pathway



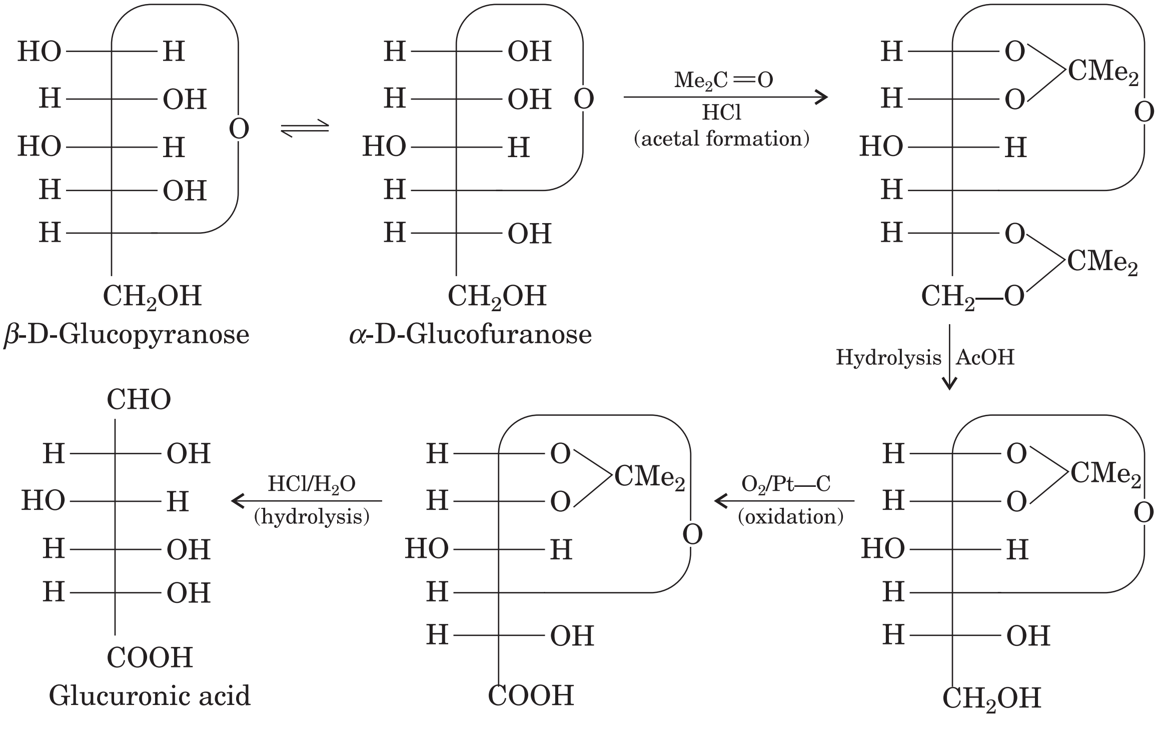
Stepwise pathway



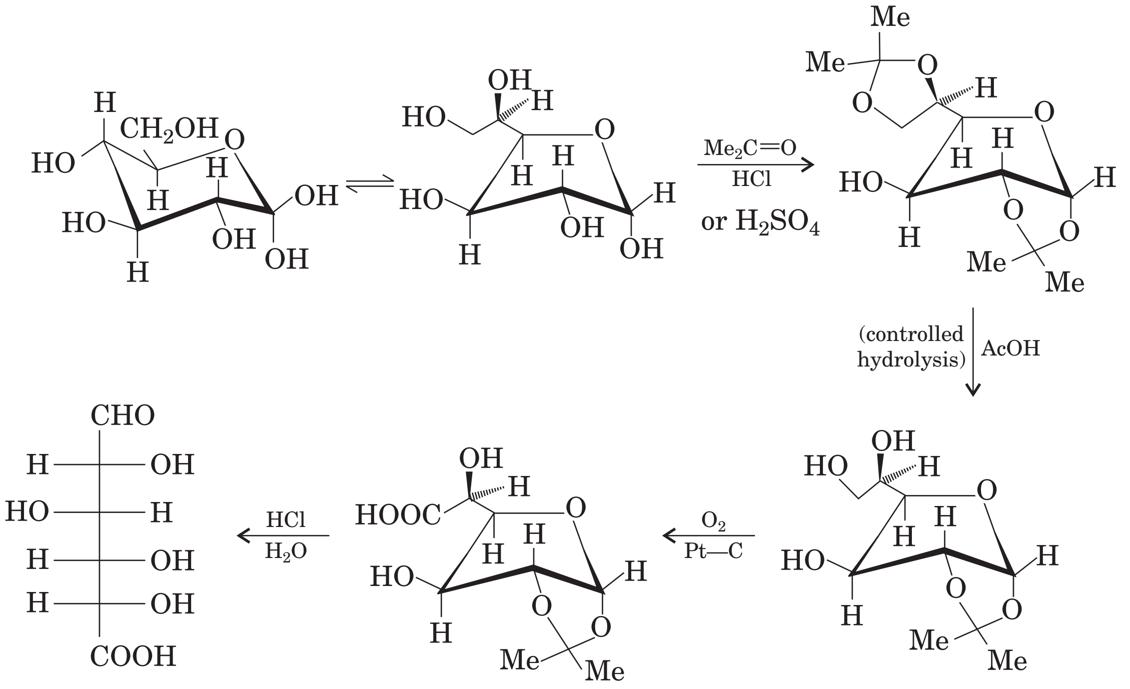
17. How would you convert D-glucose into glucuronic acid?



Solution This transformation may be carried out by oxidising selectively the —CH$_2$OH group and a general method for this oxidation involves protection of the aldehyde group, usually as the isopropylidine derivative. Acetone protects two *cis*-hydroxyl groups on adjacent carbons. In β-D-glucopyranose all the adjacent –OH groups are *trans*. Hence, to form the di-isopropylidene derivative, the ring changes size (from pyranose to furanose).

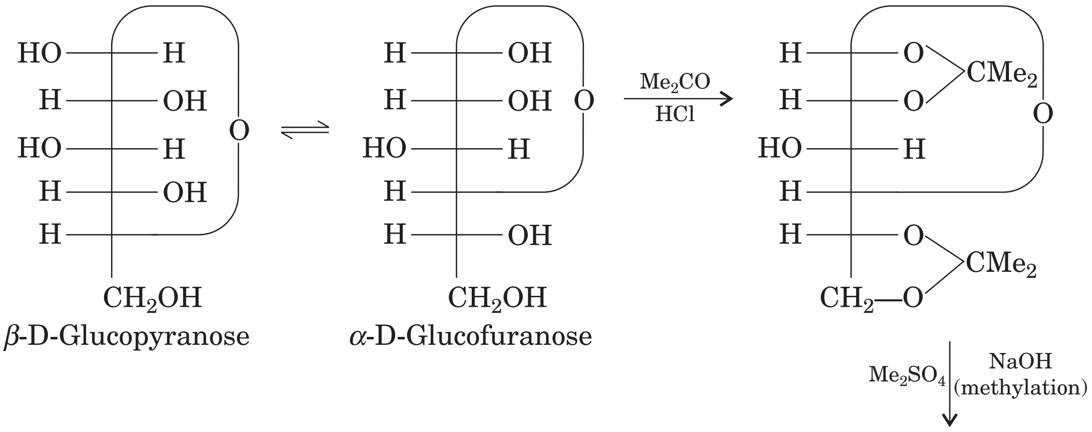


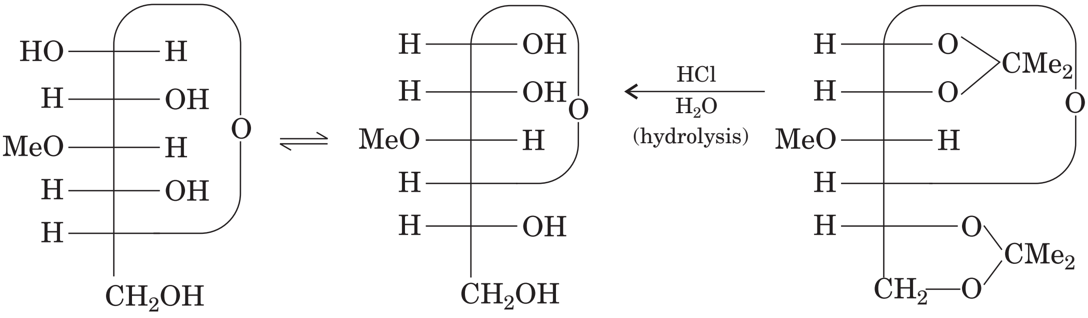
This may also be represented as follows:



18. How would you carry out selective methylation of C-3 –OH group of D-(+)-glucose? Explain why selective methylation of C-3 –OH group of D-galactose cannot be carried out.

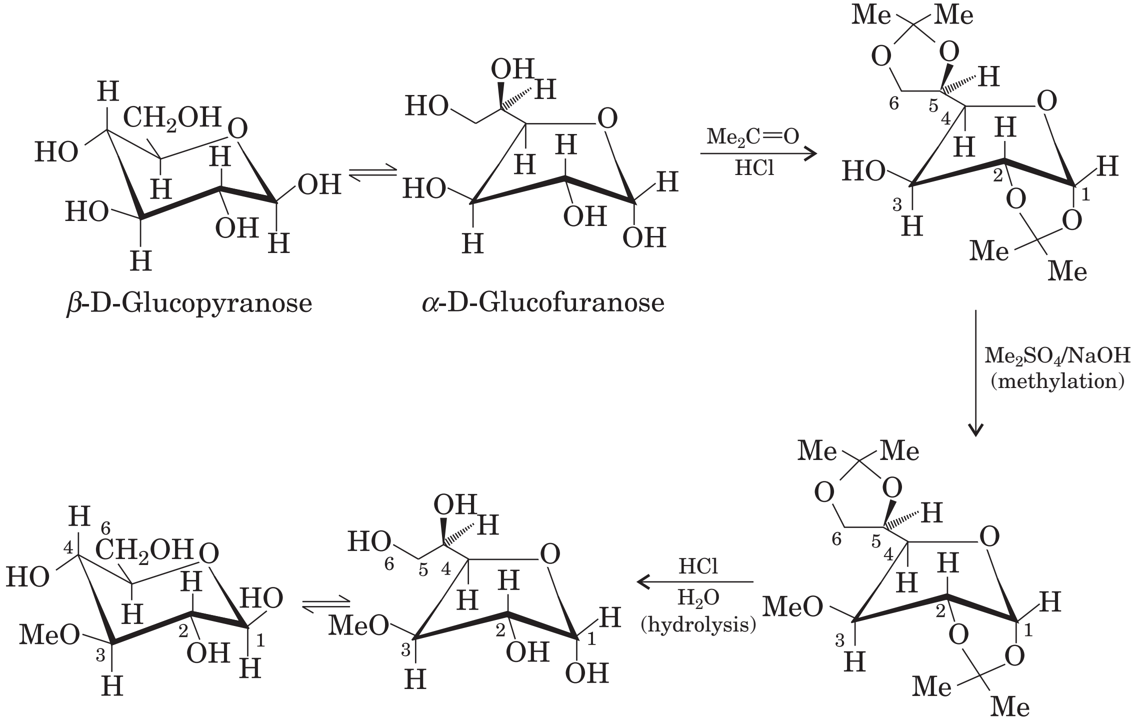
Solution Selective methylation of C-3 –OH group of D-(+)-glucose may be carried out by forming di-isopropylidene (or acetone) derivative followed by methylation and hydrolysis with hydrochloric acid.





3-*O*-Methyl-*β*-D-glucopyranose

This may also be shown as follows:

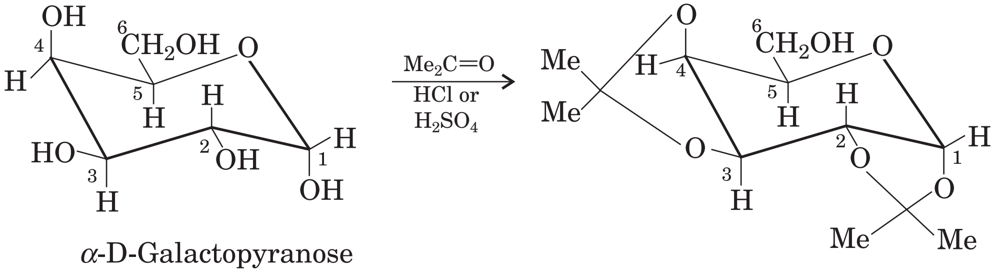


β-D-Glucopyranose

α-D-Glucofuranose

3-*O*-Methyl-*β*-D-glucopyranose

D-Galactose reacts with acetone in the presence of acid to form the di-isoprophylidene galactose through the relatively less stable α-anomer because there are two pairs of *cis* vicinal –OH groups (at C-1 and C-2 and at C-3 and C-4).



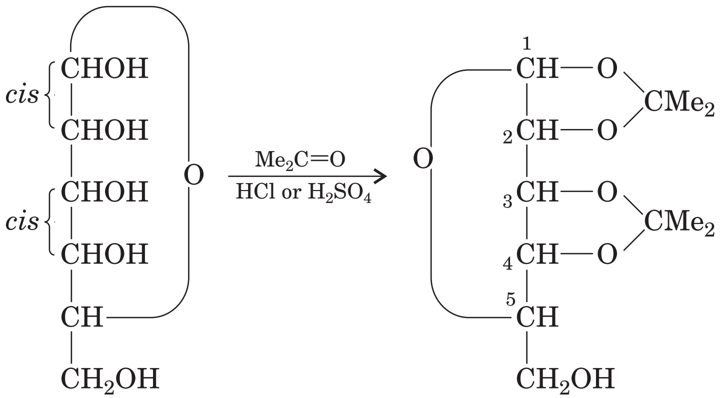
α-D-Galactopyranose

1,2 : 3,4-Di-*O*-isopropylidene-
α-D-Galactopyranose

Since the C-3 –OH in di-isopropylidene derivative is not free, methylation of C-3 –OH of D-galactose is not possible.

19. Explain why glucose, mannose, gulose, and idose can be converted to the corresponding 3-ketones *via* their di-isopropylidene derivatives, whereas allose altrose, galactose, and talose cannot be converted to the corresponding 3-ketones by the similar process.

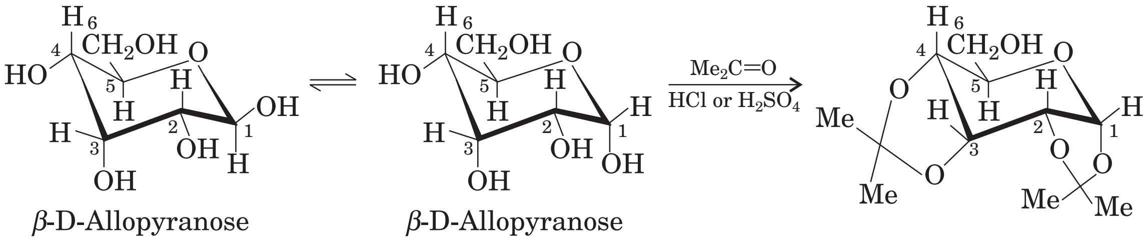
Solution The C-3 of an aldohexose can be oxidized by protecting all other —CHOH– groups and this can be done by acetone which forms isopropylidene derivative with *cis*-1,2-diols. Furthermore, because formation of the di-isopropylidene derivative is so highly favoured, this is the usual product obtained when a sugar is allowed to react with acetone in the presence of acid. Also, in order to form this di-isopropylidene derivative, the ring will, if required, change from pyranose to furanose. All of the eight diastereoisomeric D-aldohexoses can form 1,2-derivative, since the α- or β-anomeric –OH group will be *cis* with respect to the –OH group on C-2. If the –OH groups on C-3 and C-4 are *cis*, then these form the 3,4-isopropylidene derivative. Since in this case the C-3 –OH group is protected, oxidation to the 3-ketone is not possible. If, however, these two –OH groups are *trans*, the 5,6-isopropylidene derivative is formed by changing the ring from pyranose to furanose. It has the C-3 –OH group free and it can then be oxidized to the corresponding 3-ketone. The –OH groups on C-3 and C-4 are *trans* in glucose, mannose, gulcose, and idose, wheras they are *cis* in allose, altrose, galactose, and talose. Therefore, only glucose, mannose, gulose, and idose can be oxidized to the corresponding 3-ketones *via* their di-isopropylidene derivatives.



(Pyranose form
of allose, altrose, gulose,
and idose)

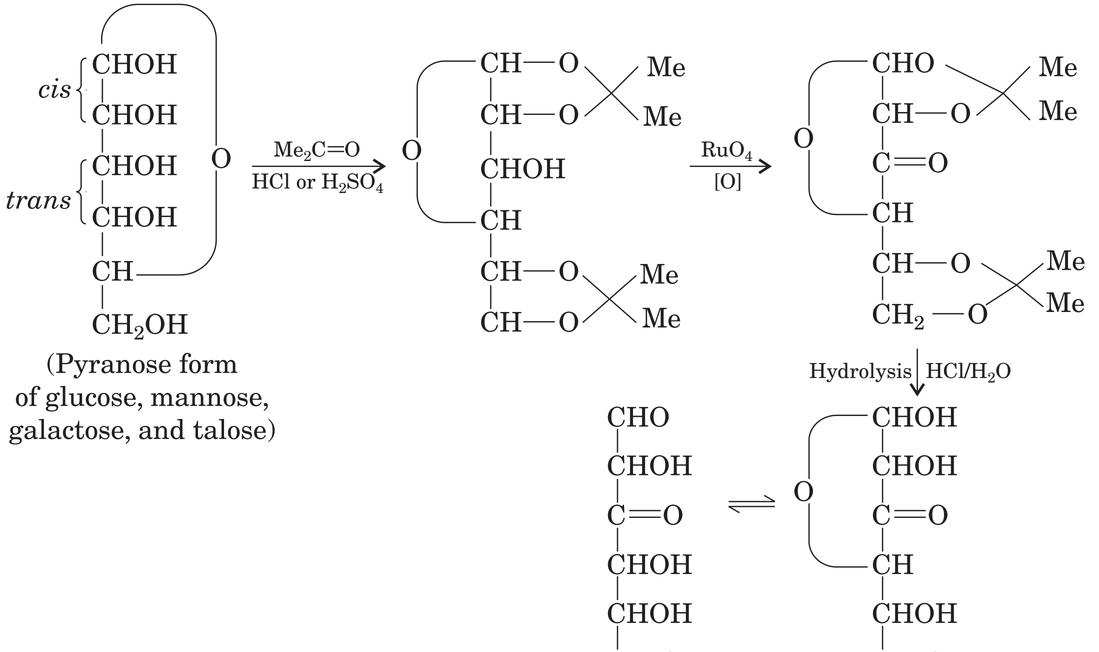
(C-3 is blocked and so, its
oxidation is not possible)

This can be shown by the chair conformation of D-allopyranose as follows:



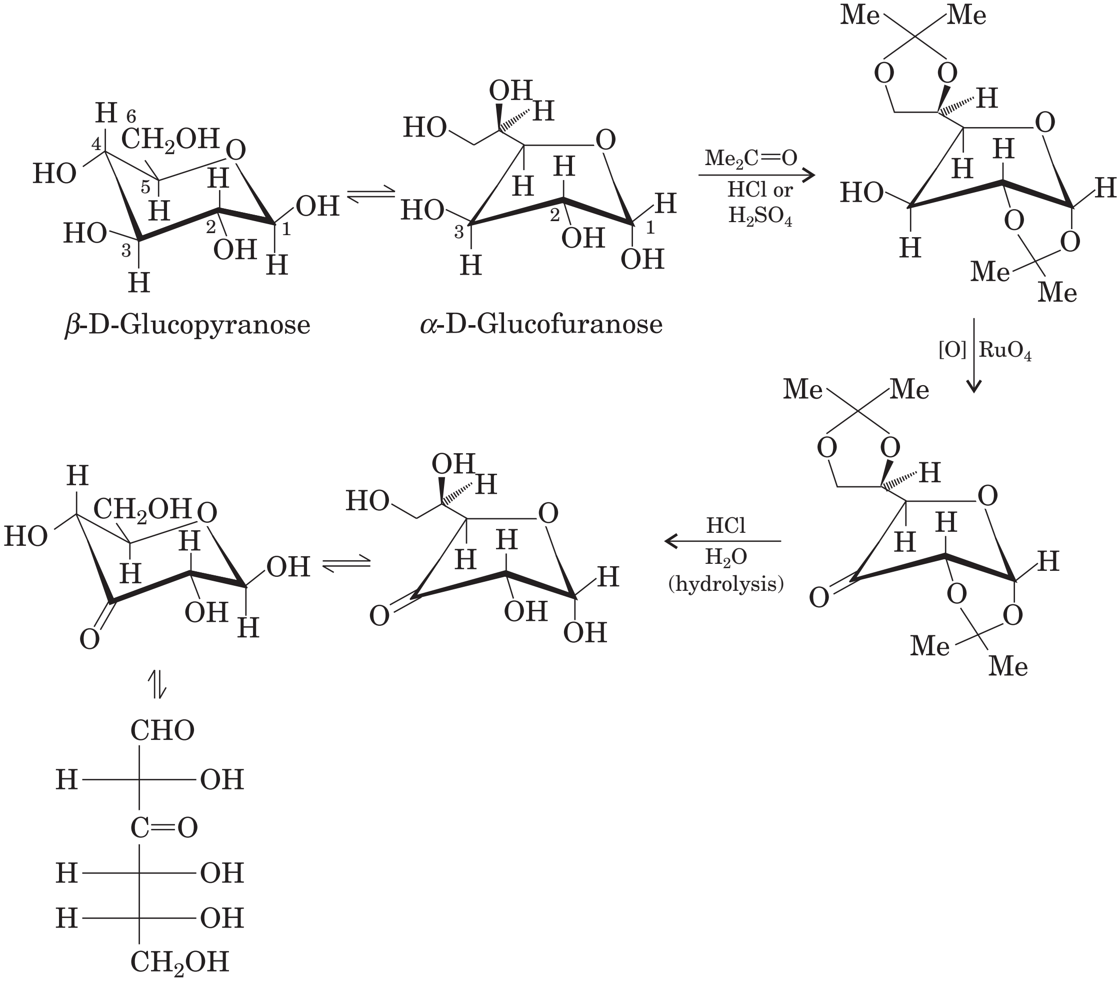
β-D-Allopyranose

β-D-Allopyranose



(Pyranose form
of glucose, mannose,
galactose, and talose)

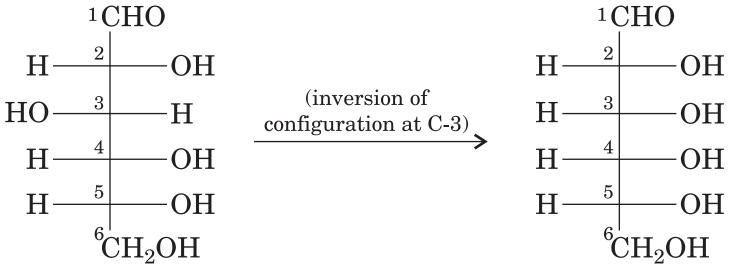
This transformation in the case of D-glucose can be shown as follows:



[It is to be noted that mild oxidising agents like DMSO/DCC, DMSO/Ac_2O, or DMSO/P_4O_{10} can also be used instead of ruthenium tetroxide (Ru_4O_4).]

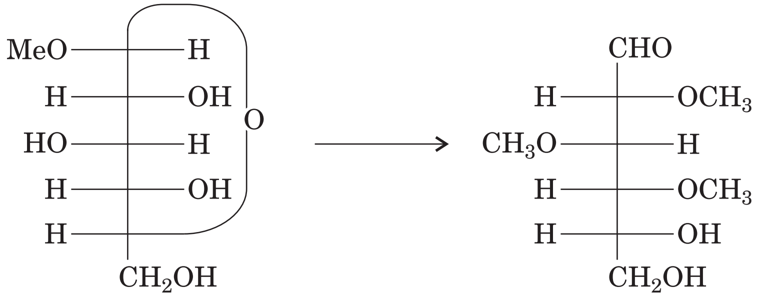
20. How would you carry out the following transformations?

(a)



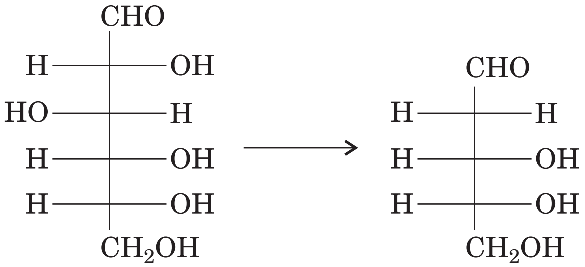
D-Glucose D-Allose

(b)



Methyl β-D-glucopyranoside 2,3,4-Tri-*O*-methyl-D-glucose

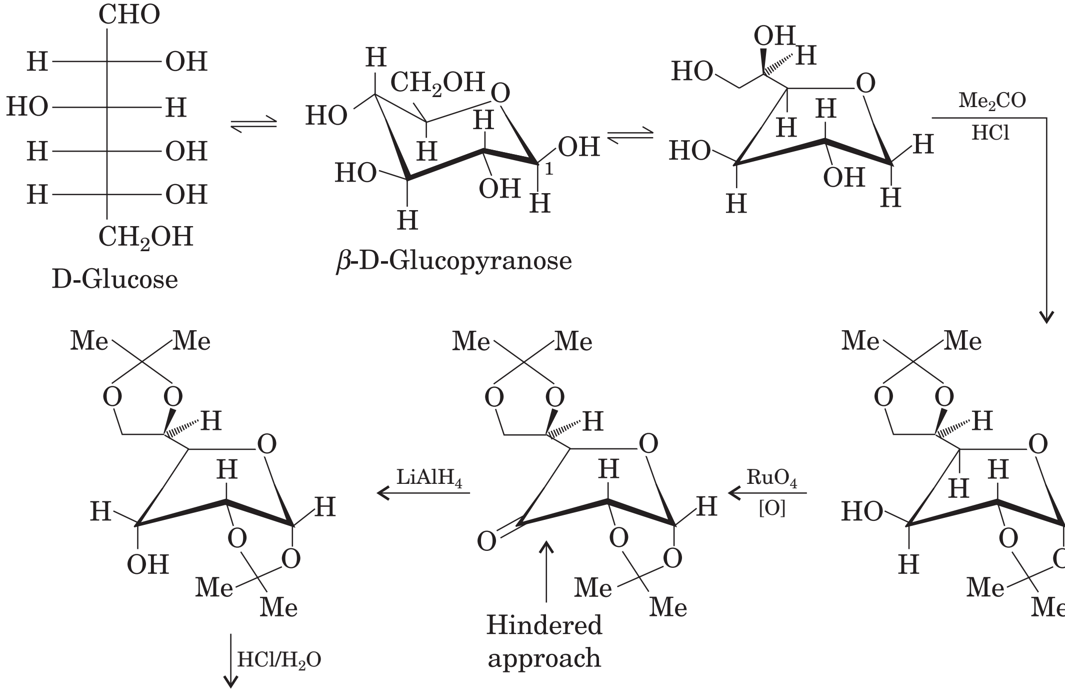
(c)

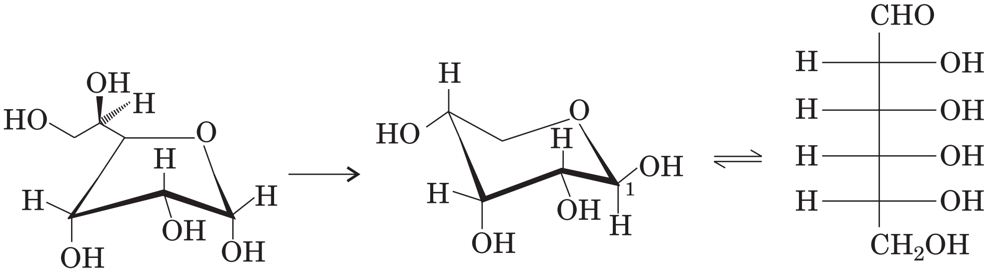


D-Glucose 2-Deoxy-D-ribose

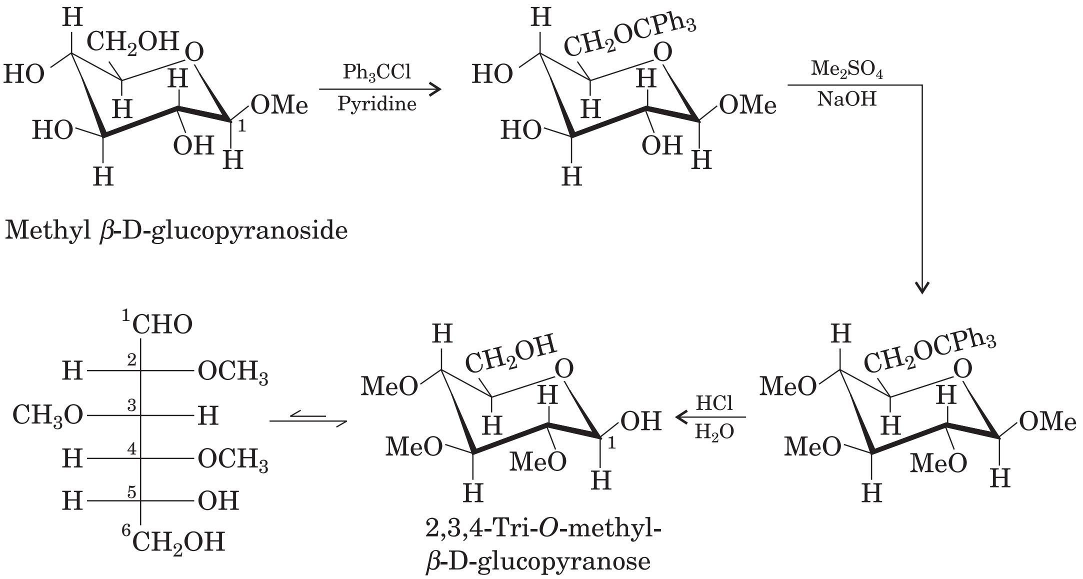
Solution

(a) This transformation may be carried out by forming the di-isopropylidene derivative of the sugar followed by oxidation and subsequent reduction involving approach of the reducing agent through the less hindered face of the carbonyl group.




β-D-Allopyranose D-Allose

(b) This transformation may be carried out as follows:

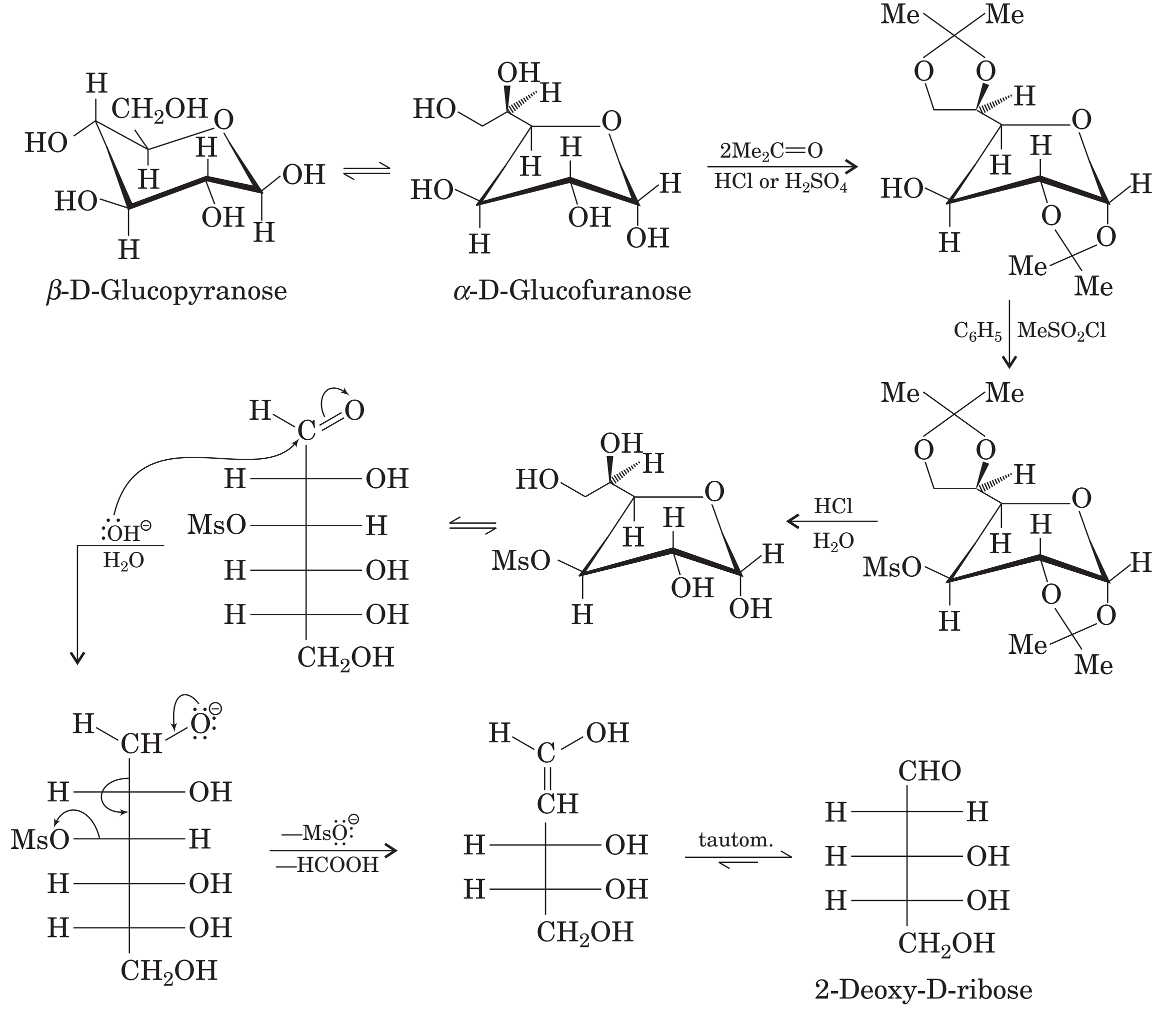


Methyl β-D-glucopyranoside

2,3,4-Tri-*O*-methyl-β-D-glucopyranose

The pyranoside is first treated with trityl chloride (Ph_3CCl) in the presence of pyridine. Only the exocyclic and the least sterically hindered —CH_2OH group undergoes etherification and becomes converted to the —CH_2OCPh_3 group. The C-6 –OH group is thereby protected from further reaction. The remaining –OH groups are then methylated with Me_2SO_4/NaOH. The resulting compound is finally hydrolyzed by dilute acid when both the trityl and the glycosidic Me groups are removed leaving C-2, C-3 and C-4 —OMe groups intact.

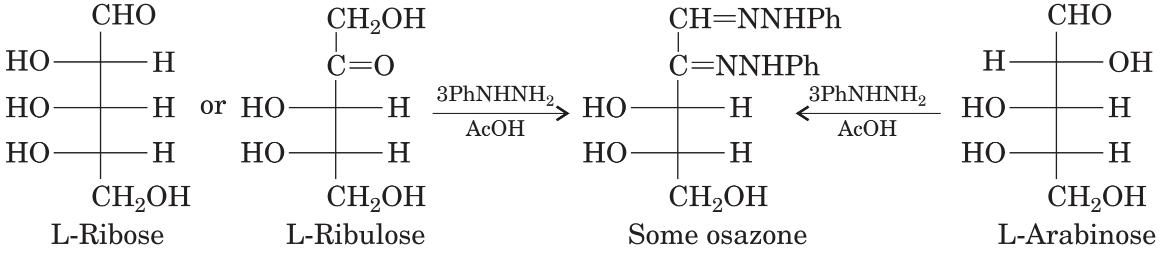
(c) This transformation may be carried out as follows:



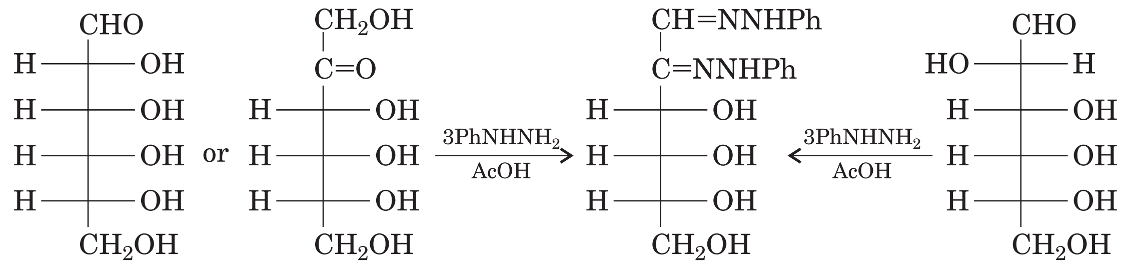
21. Identify the aldohexose and the ketohexose that form the same osazone as:
(a) L-Arabinose (b) D-Altrose (c) L-Galactose (d) D-Idose

Solution

(a) L-ribose and L-ribulose form the same osazone as L-arabinose.

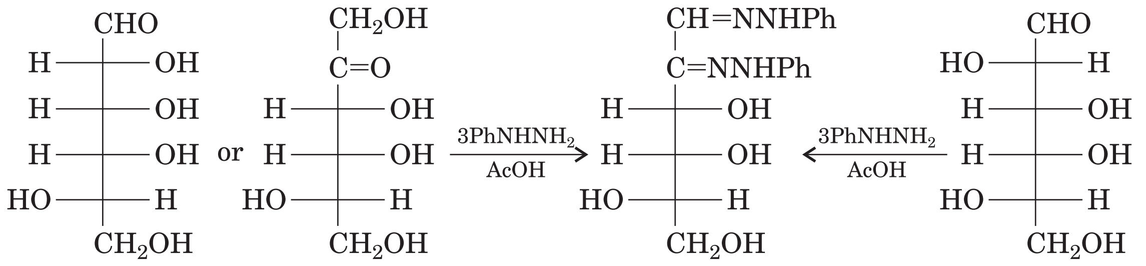


(b) D-Allose and D-psicose form the same osazone as D-altrose.



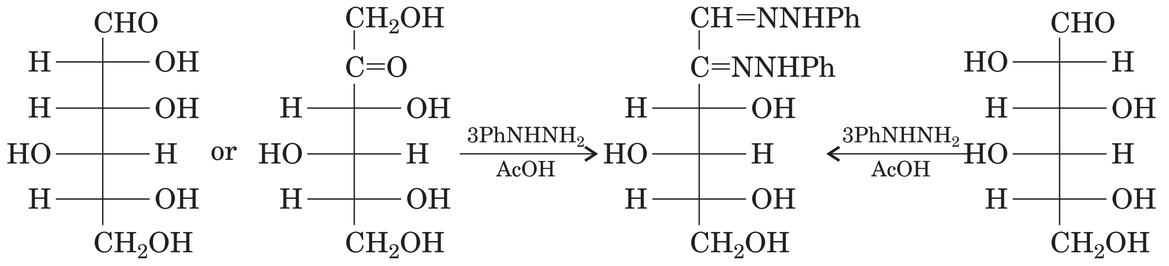
D-Allose D-Psicose Same Osazone D-Altrose

(c) L-Talose and L-tagatose form the same osazone as L-galactose.



L-Talose L-Tagatose Same Osazone L-Galactose

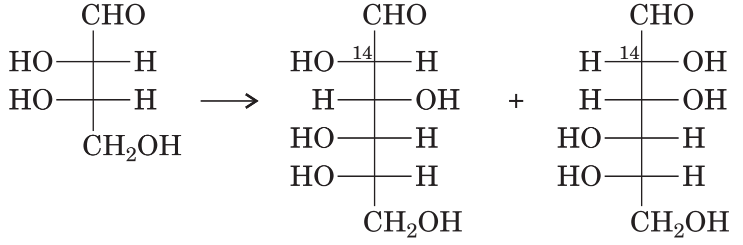
(d) D-Gulose and D-sorbose form the same osazone as D-idose



D-Gulose D-Sorbose Same Osazone D-Idose

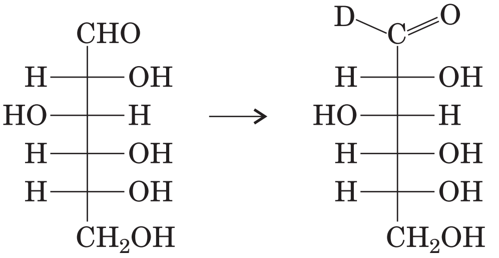
22. How would you carry out the following transformations?

(a)



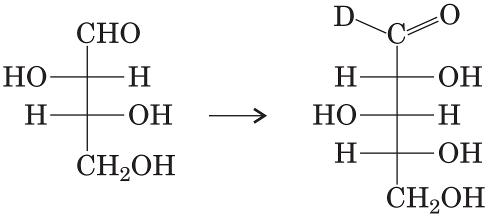
L-Erythrose L-Glucose-2-^{14}C L-Mannose-2-^{14}C

(b)



D-Glucose 1-Deuterio-D-glucose

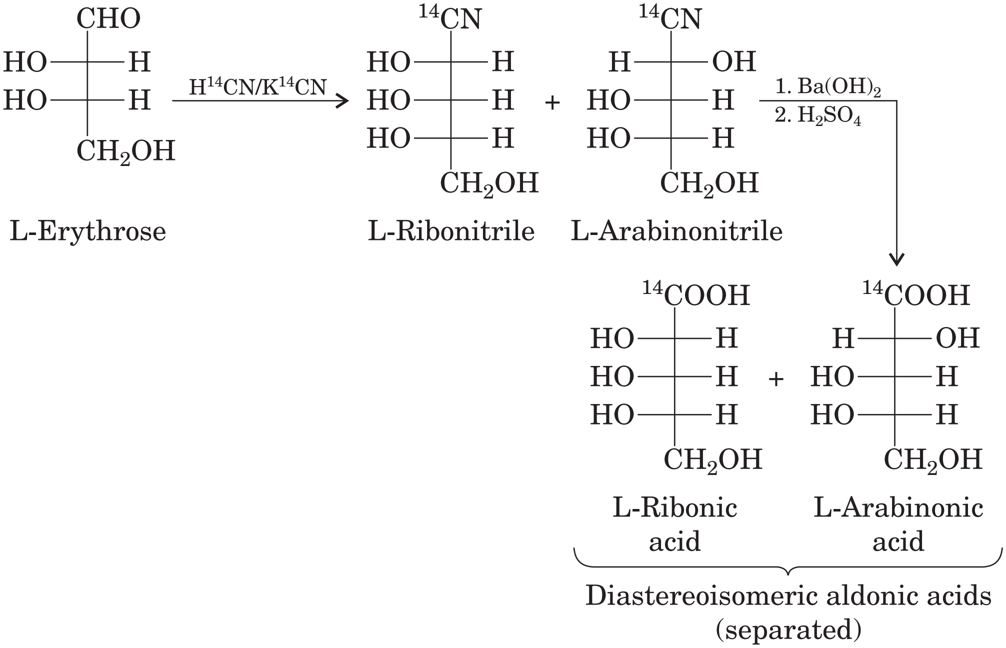
(c)

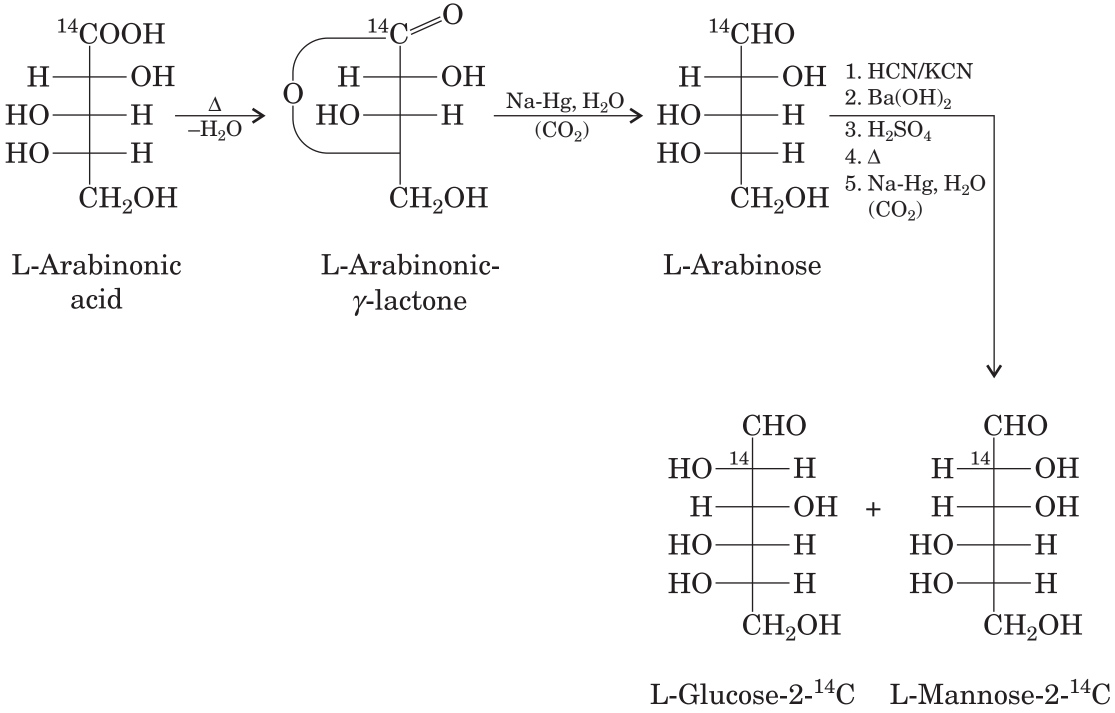


D-Threose 1-Deuterio-D-xylose

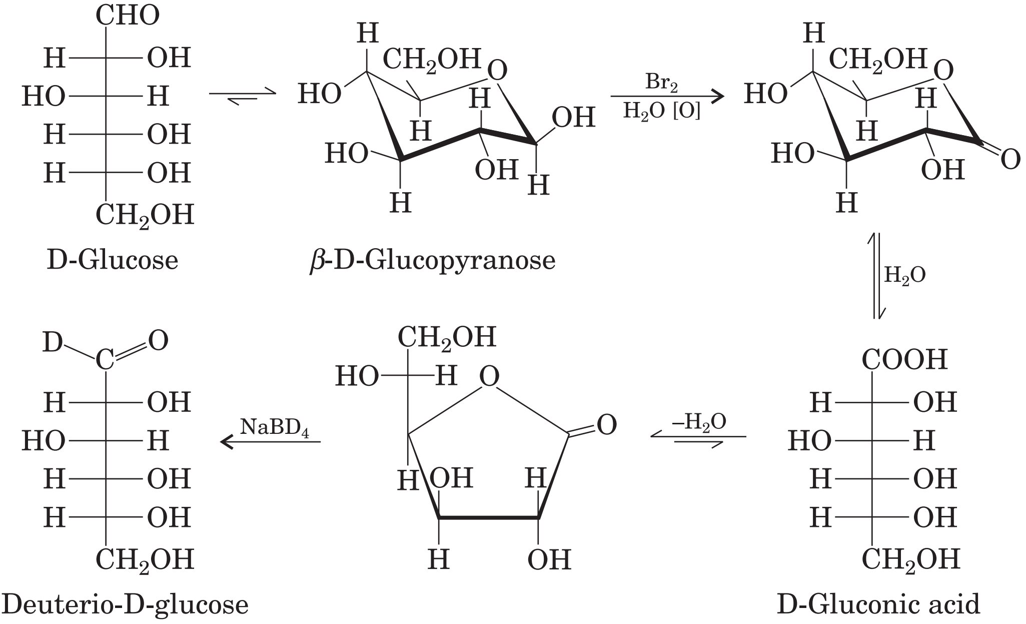
Solution

(a) This conversion may be carried out by using two successive Kiliani–Fischer syntheses as shown below:

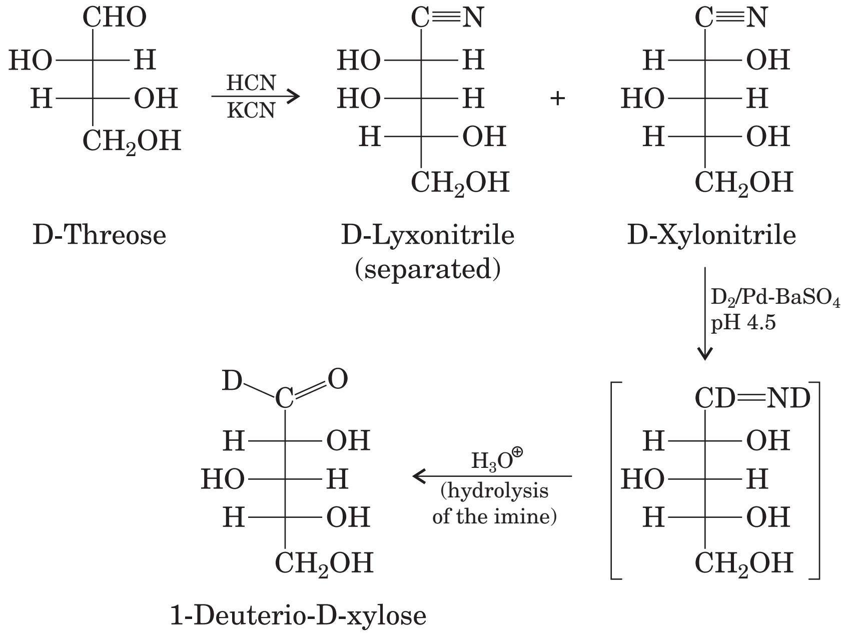



Δ
–H2O
Na-Hg, H2O
(CO2)
1. HCN/KCN
2. Ba(OH)2
3. H2SO4
4. Δ
5. Na-Hg, H2O
(CO2)
L-Arabinonic acid
L-Arabinonic-γ-lactone
L-Arabinose
L-Glucose-2-14C
L-Mannose-2-14C

(b)

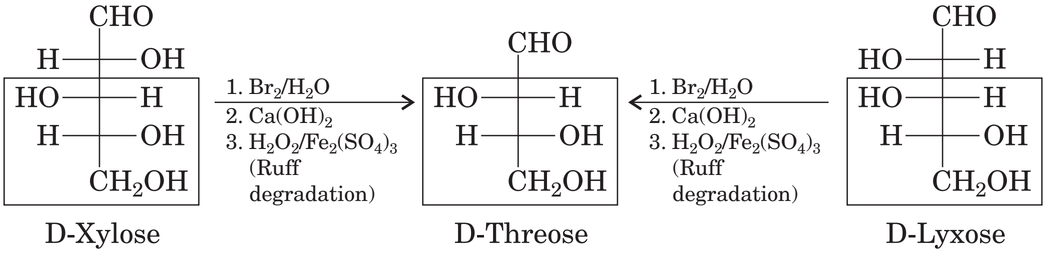

D-Glucose
β-D-Glucopyranose
Br2
H2O [O]
H2O
–H2O
NaBD4
1-Deuterio-D-glucose
D-Gluconic acid

(c)



23. Explain why the Ruff degradation of D-xylose gives the same aldopentose (D-threose) as does D-lyxose.

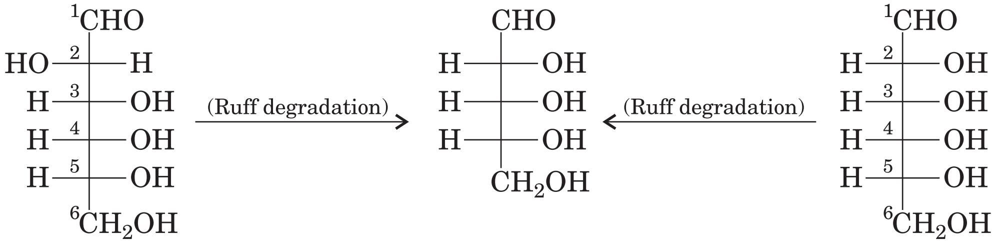
Solution In the Ruff degradation, C-2 of the aldose is converted to a —CHO group and because of this, two C-2 epimeric aldoses give the same lower aldose when subjected to Ruff degradation. Since D-xylose and D-lyxose are C-2 epimers, they give the same aldotetrose (D-threose).



24. Which two monosaccharide can be degraded by Ruff's method to: (a) D-ribose? (b) D-glyceraldehyde?

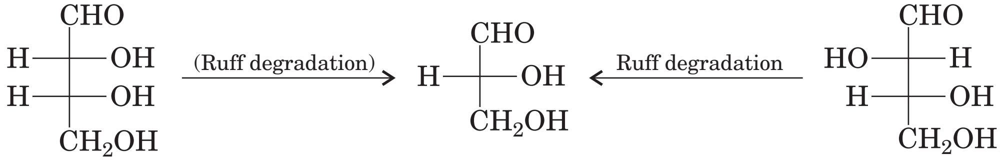
Solution

(a) D-Altrose and D-allose (C-2 epimers) can be degraded by the Ruff's method to D-ribose.



D-Altrose D-Ribose D-Allose

(b) D-Erythrose and D-threose (C-2 epimers) can be degraded by the Ruff's method to D-glyceraldehyde.



D-Erythrose D-Glyceraldehyde D-Threose

25. How would you distinguish chemically between the two compounds in each pair?

(a) L-Glucose and L-allose

(b) D-Glucose and L-mannitol

(c) D-Glucose and D-fructose

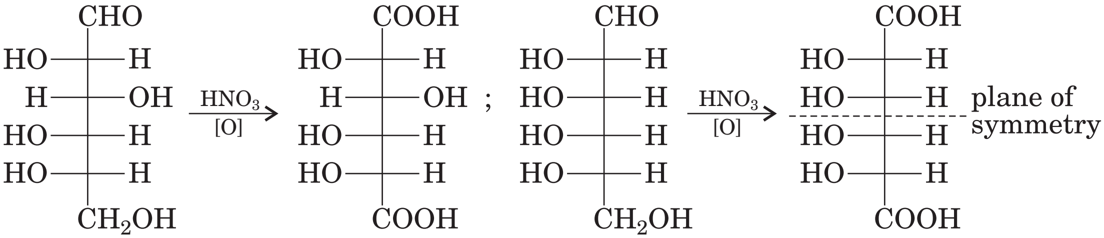
(d) β-D-Glucopyranose and methyl β-D-glucopyranoside

(e) Methyl α-D-glucopyranoside and 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose

(f) Methyl α-D-lyxofuranoside and 2-deoxy-α-D-lyxofuranoside

Solution

(a) L-Glucose on oxidation by nitric acid yields an optically active aldaric acid, whereras L-allose on similar oxidation yields an optically inactive aldaric acid.



L-Glucose L-Glucaric acid (optically active) L-Allose L-Allaric acid (optically inactive)

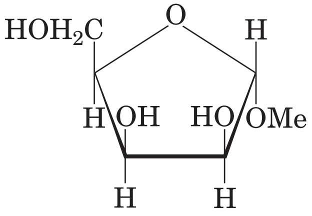
(b) Tollens' reagent or Benedict's reagent gives a positive test with D-glucose but does not react with L-mannitol.

(c) D-Glucose undergoes oxidation by B_2-H_2O and the red-brown colour of the solution disappears. D-Fructose, on the other hand, does not undergo oxidation by bromine-water (as it does not isomerize to an aldohexose in this acidic reagent).

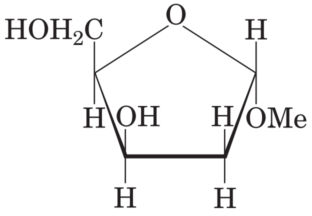
(d) β-D-Glucopyranose gives a positive test with Tollens' or Benedict's reagent, while methyl β-D-glucopyranoside does not.

(e) 2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranose gives a positive test with Tollens' or Benedict's reagent, while methyl α-D-glucopyranoside does not.

(f)



Methyl α-D-lyxofuranoside

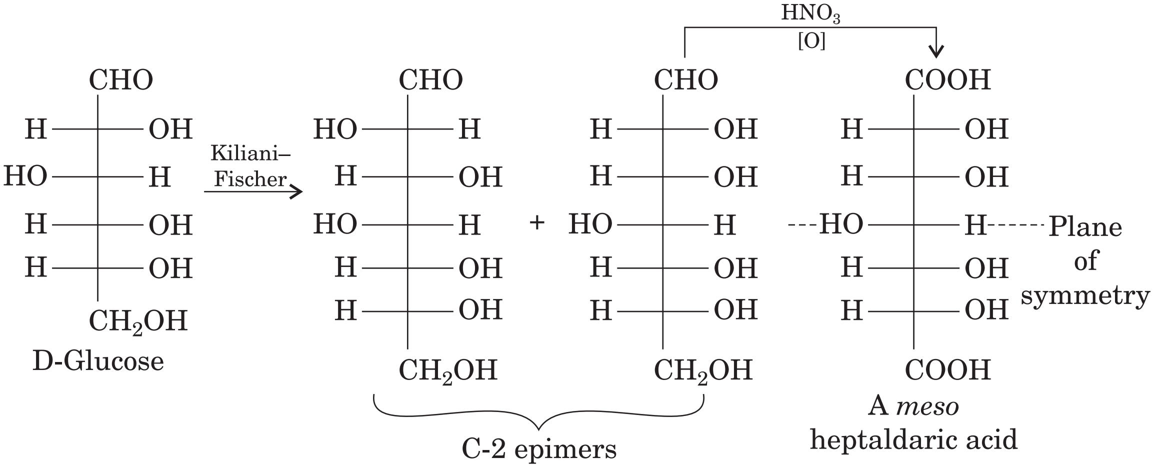


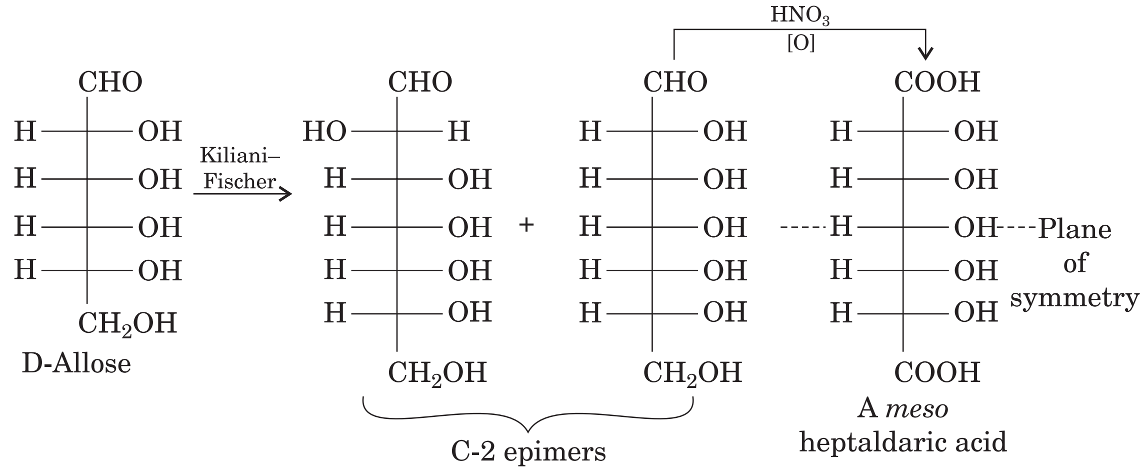
Methyl 2-deoxy-α-D-lyxofuranoside

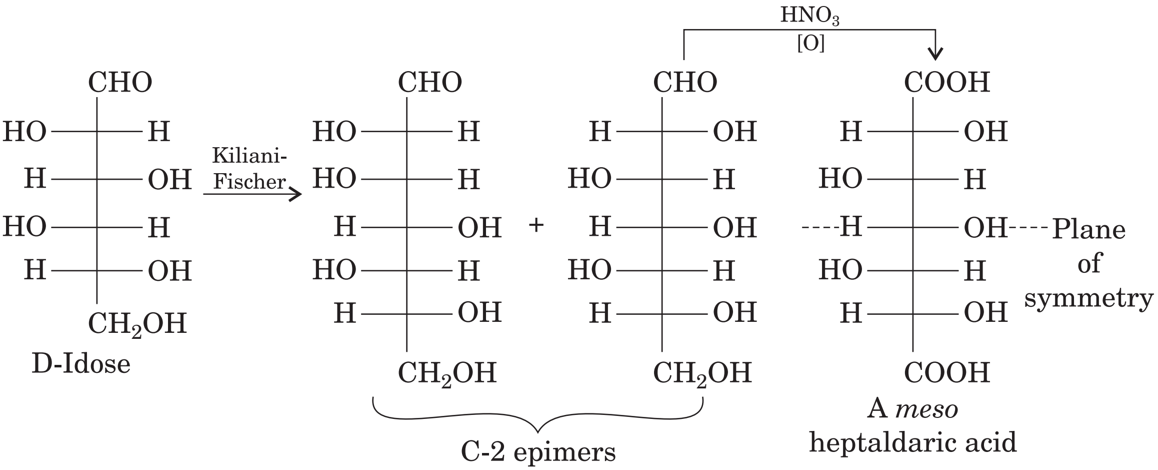
Methyl α-D-lyxofuranoside undergoes oxidation by periodic acid (because it has –OH groups on adjacent carbons) to yield an aldehyde which gives a positive test with Tollens' or Benedict's reagent. Methyl 2-deoxy-α-D-lyxofuranoside, on the other hand, does not react with periodic acid (HIO_4) as there is no glycolic moiety in the molecule.

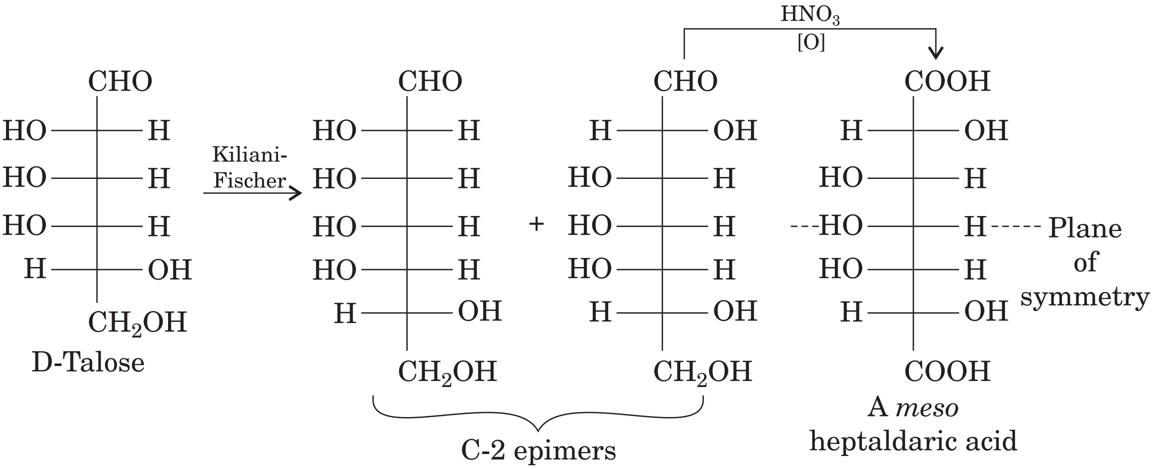
26. One of the Kiliani-Fischer step-up products of four D-aldohexoses produces a *meso*-heptaldaric acid on oxidation. Identify these aldohexoses.

Solution One of the Kiliani–Fischer step-up products of D-glucose, D-allose, D-idose, and D-talose on oxidation produces a *meso*-heptaldaric acid. This may be shown as follows:



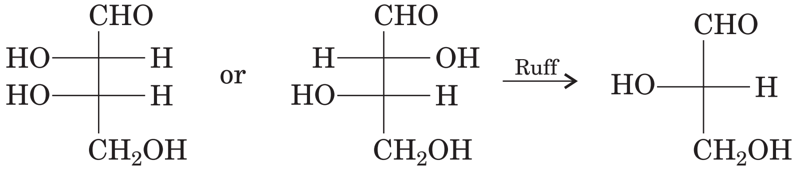

HNO3
[O]
Kiliani–Fischer
D-Allose
C-2 epimers
Plane of symmetry
A meso heptaldaric acid


HNO3
[O]
Kiliani-Fischer
D-Idose
C-2 epimers
Plane of symmetry
A meso heptaldaric acid


HNO3
[O]
Kiliani-Fischer
D-Talose
C-2 epimers
Plane of symmetry
A meso heptaldaric acid

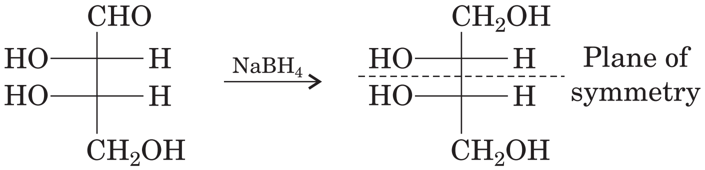
27. $NaBH_4$ reduces the aldose P to an optically inactive alditol. Ruff degradation of P yields Q, whose alditol is also optically inactive. Ruff degradation Q yield L-glyceraldehyde. Identify the aldoses P and Q.

Solution The aldose Q on Ruff degradation produces L-glyceraldehyde. Therefore, Q may be I or II.



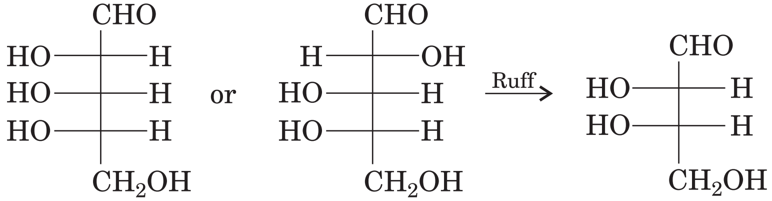
I II L-Glyceraldehyde

Q on $NaBH_4$ reduction produces an optically inactive alditol. Therefore, Q must be I (L-erythrose).



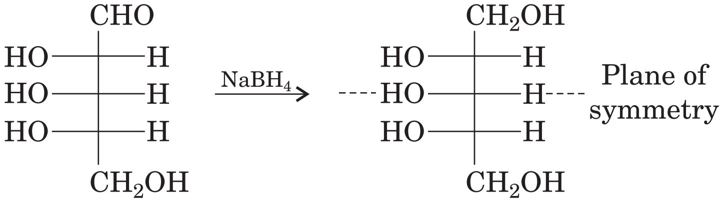
I An optically inactive alditol

Ruff degradation of P forms Q. Therefore, P may be III or IV.



III IV Q

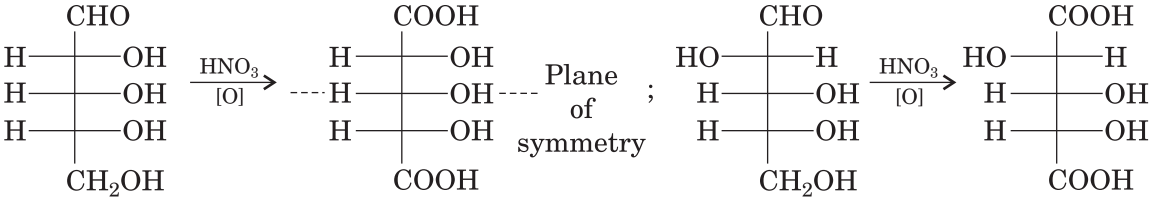
Now, P on $NaBH_4$ reduction produces an optically inactive alditol. Therefore, P must be III (L-ribose).



III An optically inactive alditol

28. The aldopantoses D-ribose and D-arabinose yield the same osazone with phenylhydrazine and yield a *meso* and an active aldaric acid, respectively, on HNO_3 oxidation. Predict their structures.

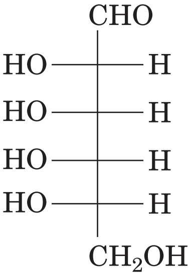
Solution Since these aldopentoses yield the same osazone, they must be C-2 epimers. Now, D-ribose yields a *meso*-aldaric acid. Hence, there is a configurational symmetry about the chirality centres C-2, C-3 and C-4 of D-ribose. There is no configurational symmetry about these chirality centres of D-arabinose because D-arabinose yields an active aldaric acid on oxidation. Therefore, I is the structure of D-ribose and II is the structure of D-arabinose.



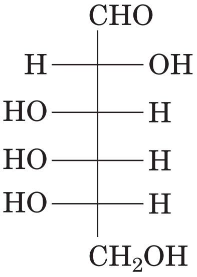
I A *meso* aldaric acid II An active aldaric acid

29. X, Y and Z are three L-aldohexoses. X and Y yield the same optically active alditol on catalytic hydrogenation. However, they yield different osazones when treated with phenylhydrazine. Y and Z give the same osazone but different alditols. Identify X, Y and Z.

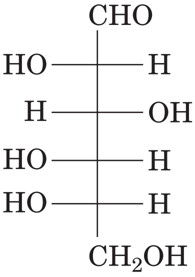
Solution X, Y and Z are three L-aldohexoses. Hence, they are any three of the following six L-aldohexoses.



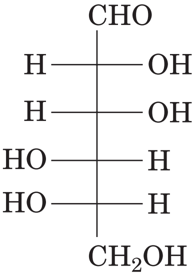
L-Allose



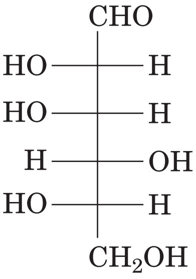
L-Altrose



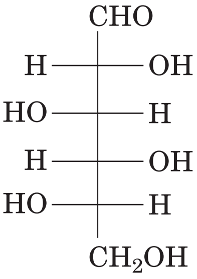
L-Glucose



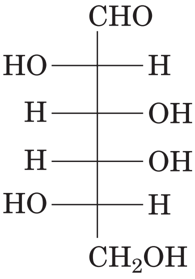
L-Mannose



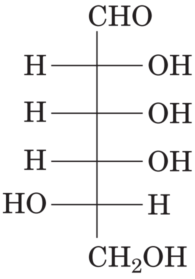
L-Gulose



L-Idose

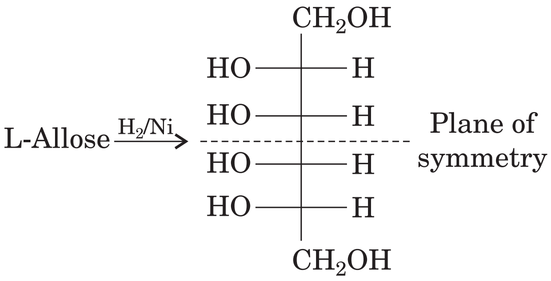


L-Galactose



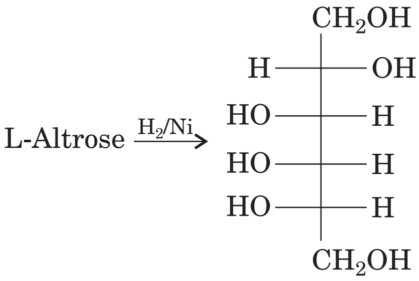
L-Talose

Now, the alditols obtained by catalytic reduction of these eight aldohexoses are as follows:

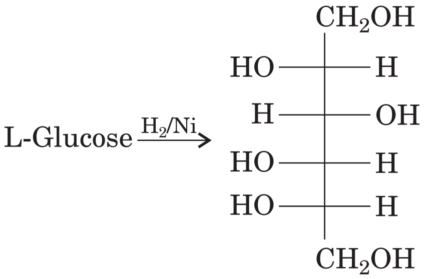


(Optically inactive)

;



(Optically active)



(Optically active)

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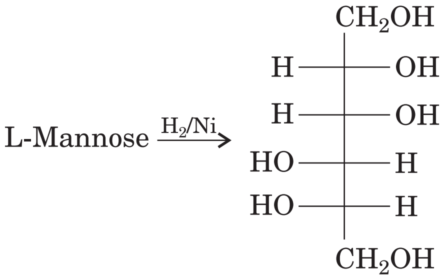
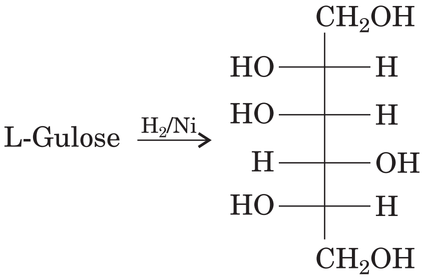


(Optically active)



(Optically active)

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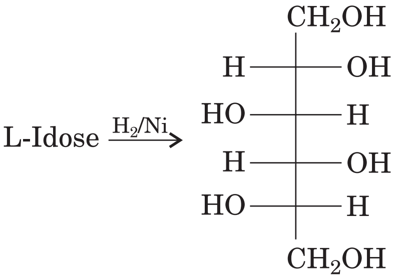
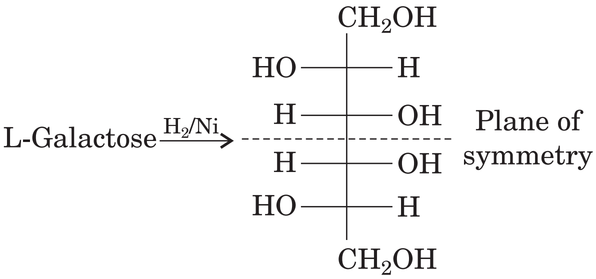


(Optically active)



(Optically inactive)

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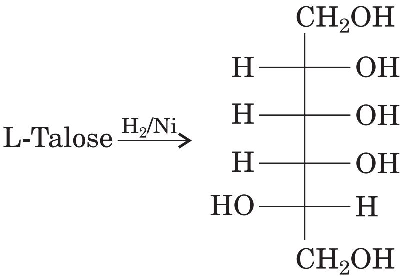
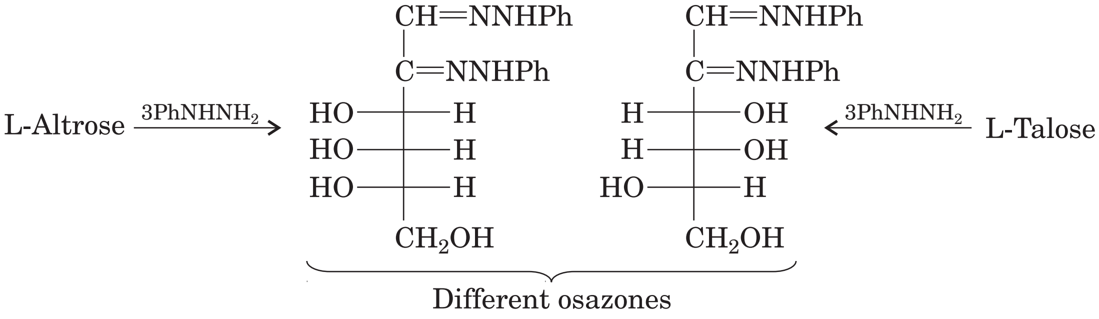


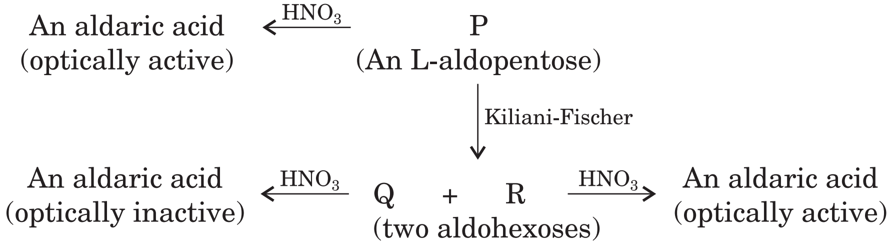
(Optically active)

From the structures of the alditols it becomes evident that L-altrose and L-talose give the same active alditol. Since X and Y produce the same active alditol, these are L-altrose and L-talose. Since they are not C-2 epimers, they form different osazones.



Y and Z give the same osazone but different aditols. L-Altrose and L-allose give the same osazane (since they are C-2 epimers) but different alditols. Again, L-talose and L-galactose give the same osazone (as they are C-2 epimers) but different alditols. Therefore, if Y is L-altrose, Z is L-allose and X is L-talose and if Y is L-talose, Z is L-galactose and X is L-altrose.

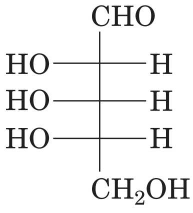
30.



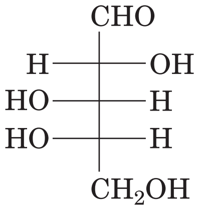
Identify P, Q and R.

Solution

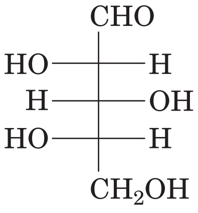
There are four L-aldopentoses:



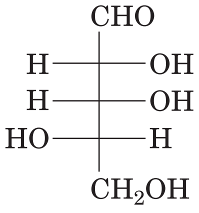
L-Ribose



L-Arabinose

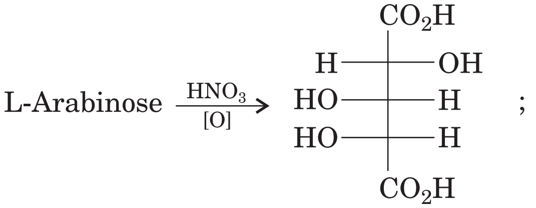


L-Xylose

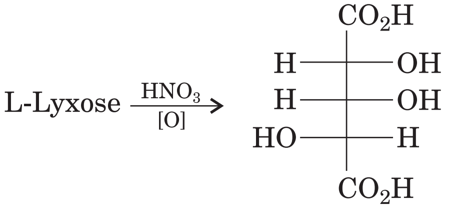


L-Lyxose

Among these four aldopentoses only L-arabinose and L-Lyxose give two optically active aldaric acids on oxidation.



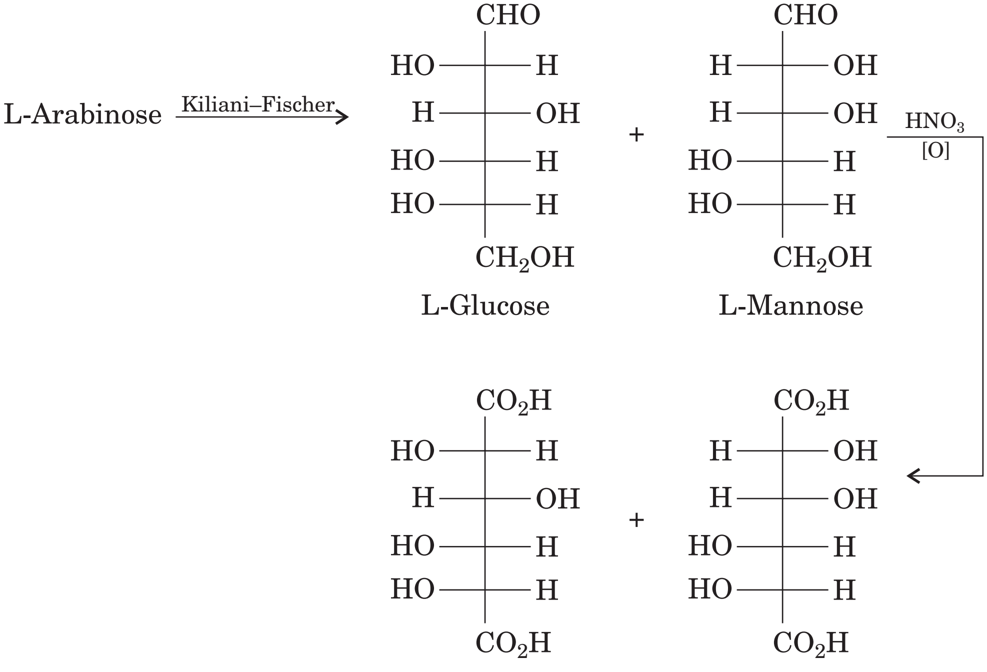
An aldaric acid
(optically active)



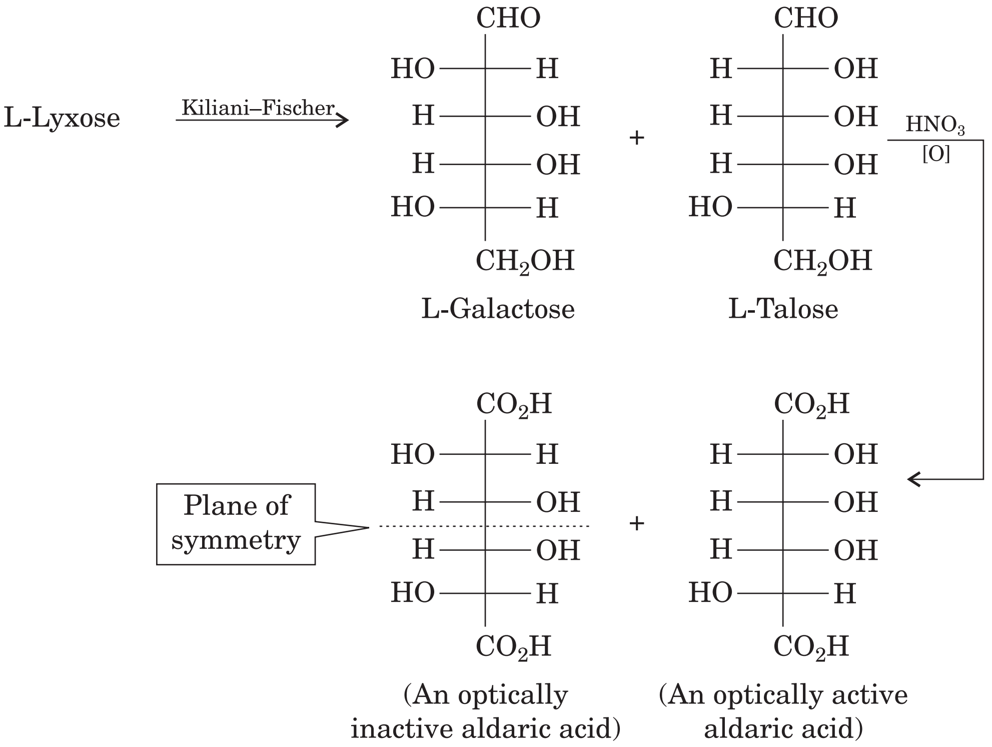
An aldaric acid
(optically active)

Therefore, the aldopentose P may be L-arabinose or L-lyxose.

A Kiliani-Fischer step-up of L-arabinose gives L-glucose and L-mannose, both of which on oxidation produce optically active aldaric acid. But a Kiliani-Fischer step-up of L-lyxose gives L-galactose and L-talose. L-Galactose on oxidation yields an optically inactive aldaric acid, while L-talose or oxidation yields an optically active aldaric acid. Therefore, the aldopentose P is L-lyxose and the aldohexoses Q and R are L-galactose and L-talose respectively.



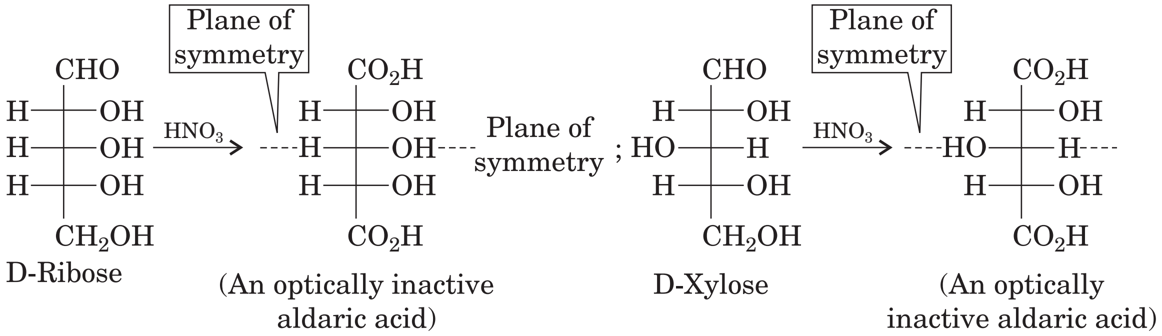
(optically active aldaric acids)


L-Lyxose
Kiliani–Fischer
L-Galactose
+
L-Talose
HNO$_3$
[O]
Plane of symmetry
(An optically inactive aldaric acid)
(An optically active aldaric acid)

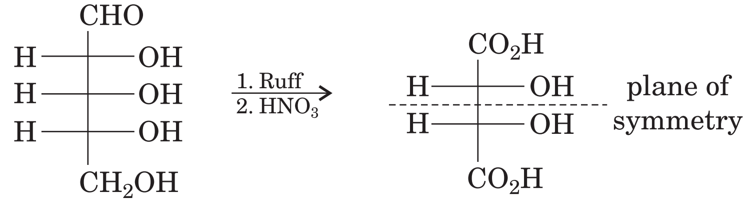
31. III (An optically active aldaric acid) $\xleftarrow[\text{2. } HNO_3]{\text{1. Ruff}}$ I A D-aldopentose $\xrightarrow{HNO_3}$ II (An optically inactive aldaric acid)

Identify the aldopentose I from the above observations.

Solution Among the four possible D-aldopentoses only D-ribose and D-xylose produce optically inactive aldaric acid on oxidation. Hence, the D-aldopentose I may be D-ribose or D-xylose.

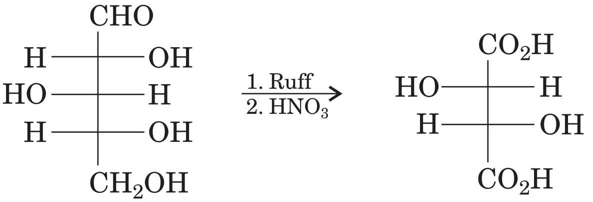


Now, the Ruff degradation followed by HNO_3 oxidation of D-ribose produces an optically inactive aldaric acid, whereas D-xylose, when treated similarly, produces an optically active aldaric acid (III). Therefore, the D-aldopentose is D-xylose.



D-Ribose

(An optically inactive aldaric acid)

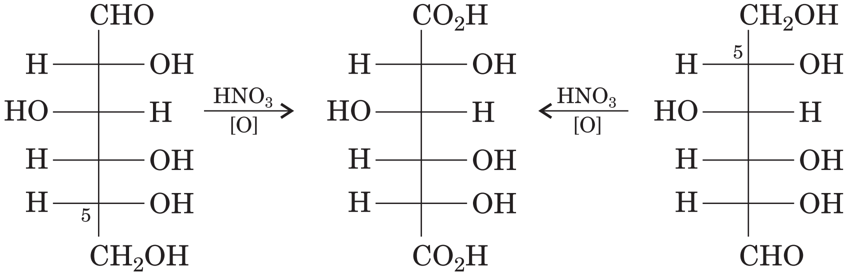


D-Xylose

(An optically active aldaric acid)

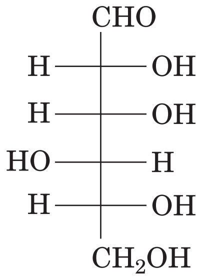
32. **D-Glucose and L-gulose undergo oxidation by HNO_3 to give the same aldaric acid and D-idose give the same osazone as that of D-gulose. If the configuration of D-glucose is known, then write down the more stable chair conformation of α-D-idopyranose.**

Solution Since D-glucose and L-gulose give the same dicarboxylic acid on oxidation, the configuration of L-gulose is that obtained by interchanging the end groups (—CHO and —CH_2OH) of D-glucose.



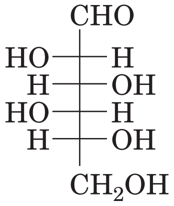
D-Glucose L-Gulose

Now, D-gulose is the enantiomer of L-gulose. Therefore, the configuration of D-gulose is:



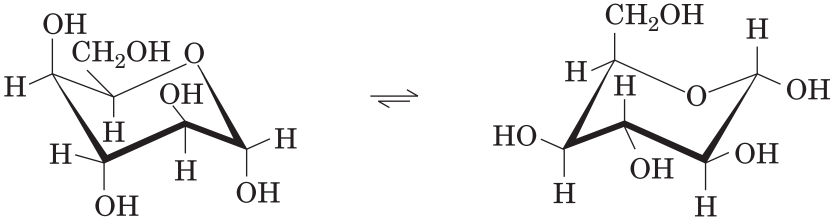
D-Gulose

Now, D-idose is the C-2 epimer of D-gulose because they form the same osazone with phenylhydrazine. Therefore, the configuration of D-idose is:



D-Idose

The more stable chair conformation of α-D-idopyranose is the one in which only the bulkiest group, —CH_2OH, occupies an axial position.

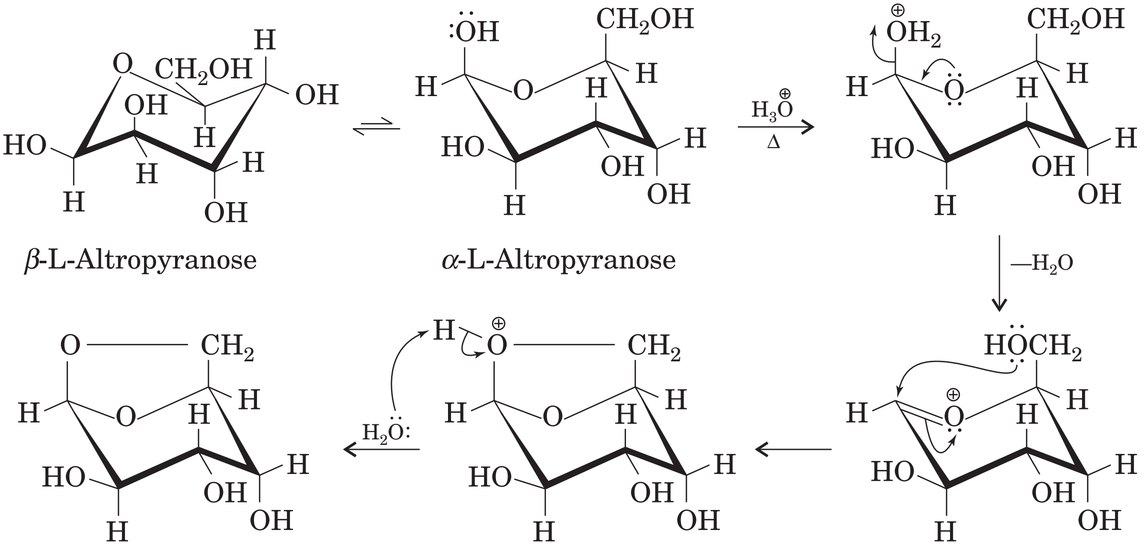


(Less stable conformation) (More stable conformation)

α-D-Idopyranose

33. When L-altrose is heated with dilute acid, a nonreducing anhydro sugar ($C_6H_{10}O_5$) known as 1,6-anhydro-L-altropyranose is obtained. Predict the structure of the anhydro sugar and explain its formation. How can it be converted to 2,3,4-tri-*o*-methyl-L-altrose? Explain why this anhydro sugar is a non-reducing one.

Solution The anhydro sugar is obtained through the conformation in which the —CH_2OH group is axial. The mechanism for the acid-catalyzed dehydration of β-L-altropyranose is as follows:

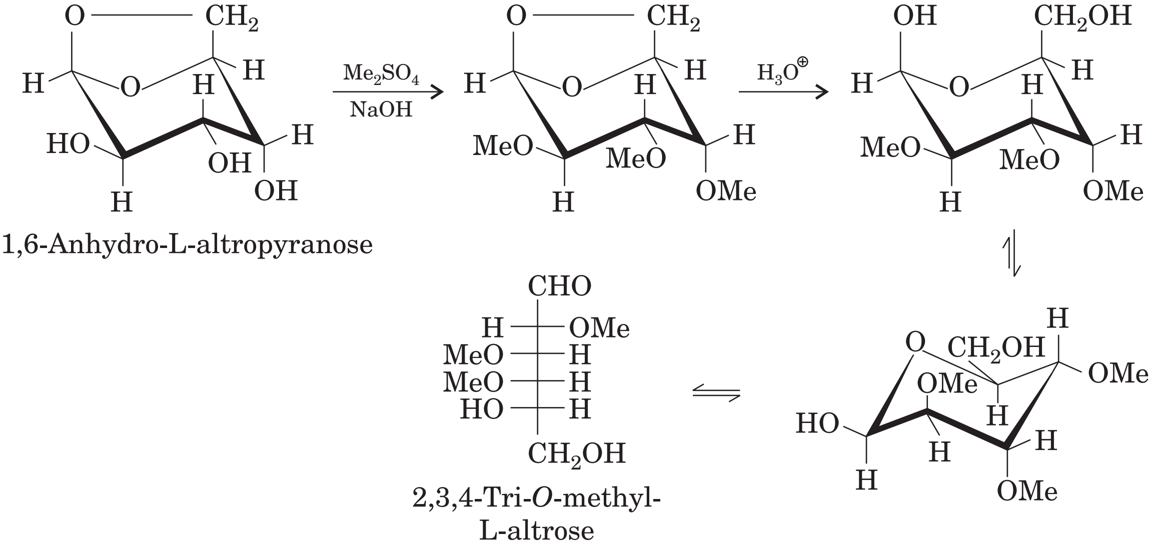


β-L-Altropyranose

α-L-Altropyranose

1,6-Anhydro-L-altropyranose
(an anhydro sugar)

This anhydro sugar can be converted to 2,3,4-tri-*O*-methyl-L-altrose by methylation followed by acid hydrolysis.



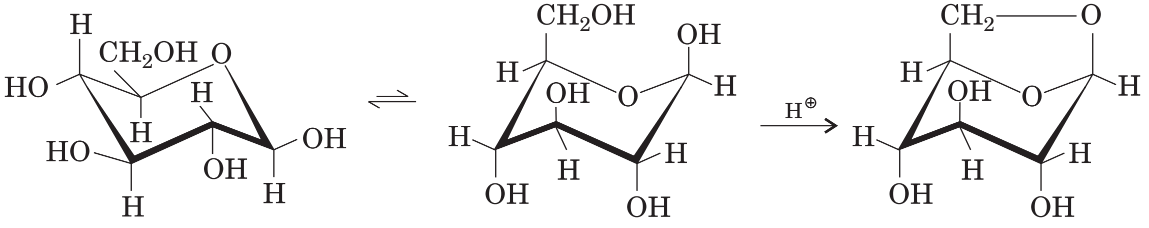
1,6-Anhydro-L-altropyranose

2,3,4-Tri-*O*-methyl-
L-altrose

Since the anhydro sugar is, in fact, an acetal, it is a nonreducing sugar.

34. Explain why the formation of an anhydro sugar from D-glucose requires a much drastic condition.

Solution The formation of an anhydro sugar requires that the sugar must adopt a chair conformation with the —CH_2OH group axial. With *β*-D-glucopyranose (the more stable anomer), however, it requires that all the four –OH groups become axial and therefore, the reaction (acid-catalyzed dehydration) must proceed through a very much unstable conformation. For this reason, the formation of an anhydro sugar from D-glucose requires a much drastic condition.

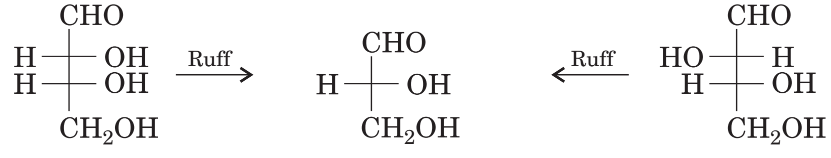


β-D-Glucopyranose

(Very unstable conformation:
all the groups are axial)

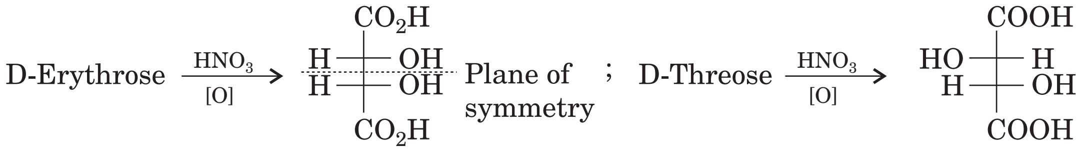
35. The two aldohexoses I and II react with phenylhydrazine to yield the same osazone. An optically inactive aldaric acid in obtained when I is oxidized by HNO_3. I or II gives the same aldopentose III when subjected to Ruff degradation. III on nitric acid oxidation yields an optically active aldaric acid. Ruff degradation of III forms IV, which on HNO_3 oxidation, produces an optically active aldaric acid. Ruff degradation of IV form (+)-glyceraldehyde. Identify I, II, III and IV.

Solution Since (+)-glyceraldehyde belongs to the D family, the aldotetrose IV may be D-erythrose or D-threose.



D-Erythrose D-(+)-Glyceraldehyde D-Threose

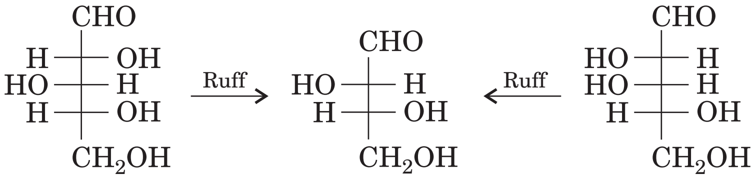
IV on HNO_3 oxidation produces an optically active aldaric acid. Therefore, IV must be D-therose.



(An optically
inactive aldaric acid)

(An optically
active aldaric acid)

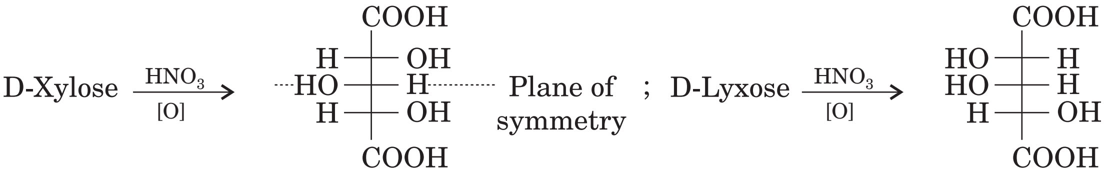
Ruff degradation of III form IV. Therefore, III may be D-xylose or D-lyxose.



IV

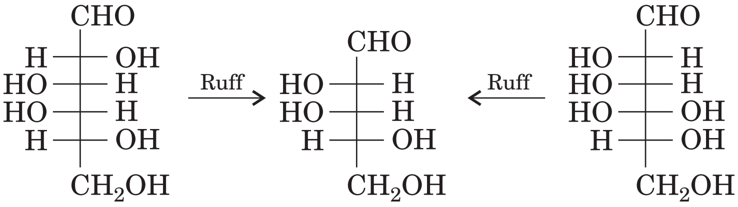
D-Xylose D-Threose D-Lyxose

III on HNO_3 oxidation produces an optically active aldaric acid. Therefore, III must be D-lyxose.



(An optically inactive aldaric acid) (An optically active aldaric acid)

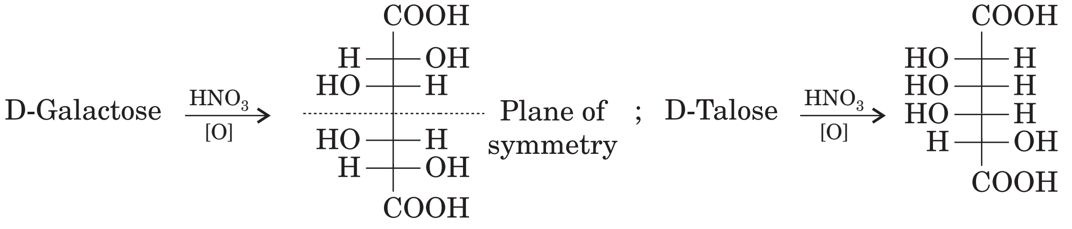
Ruff degradation of either I or II yields III. Therefore, I and II are D-galactose and D-talose.



III

D-Galactose D-Lyxose D-Talose

When I is oxidized by HNO_3, an optically inactive aldaric acid is obtained. Therefore, I must be D-galactose. Then, II must be D-talose.

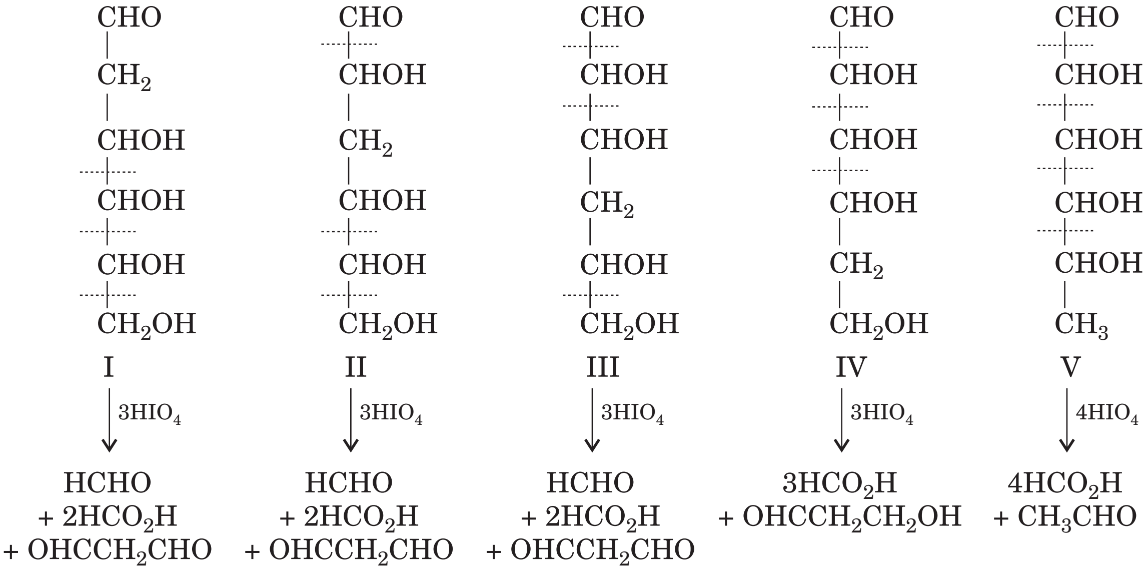


(An optically inactive aldaric acid) (An optically active aldaric acid)

D-galactose and D-talose are C-2 epimers, and so, they form the same phenylosazone.

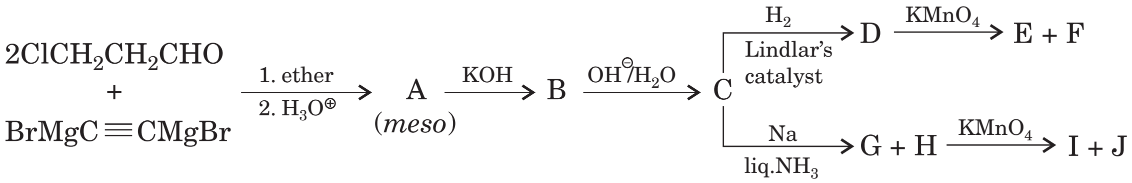
36. Compound A ($C_6H_{12}O_5$), on oxidation with bromine-water produces B ($C_6H_{12}O_6$). A forms a tetraacetate with acetic anhydride and is reduced by HI to *n*-hexane. Oxidation of A with HIO_4 yields, among other products, 1 molecule of formaldehyde and 2 molecules of formic acid. What are the possible structures of A?

Solution Formation of a tetraacetate shows the presence of four hydroxyl group in the molecule. Oxidation of A by Br_2-H_2O to give an acid with the same number of carbon atoms and the fact that A ($C_6H_{12}O_5$) adds one oxygen to give the acid B ($C_6H_{12}O_6$) indicate that A is an aldehyde. Reduction of A with HI to *n*-hexane shows that A has the carbon skeleton consists of six carbon atoms in a straight chain. Therefore, the molecular formula $C_6H_{12}O_5$ suggests that A is a deoxy-sugar and it may have any one of the following structures obtained by shifting the —CH_2— group down the chain.



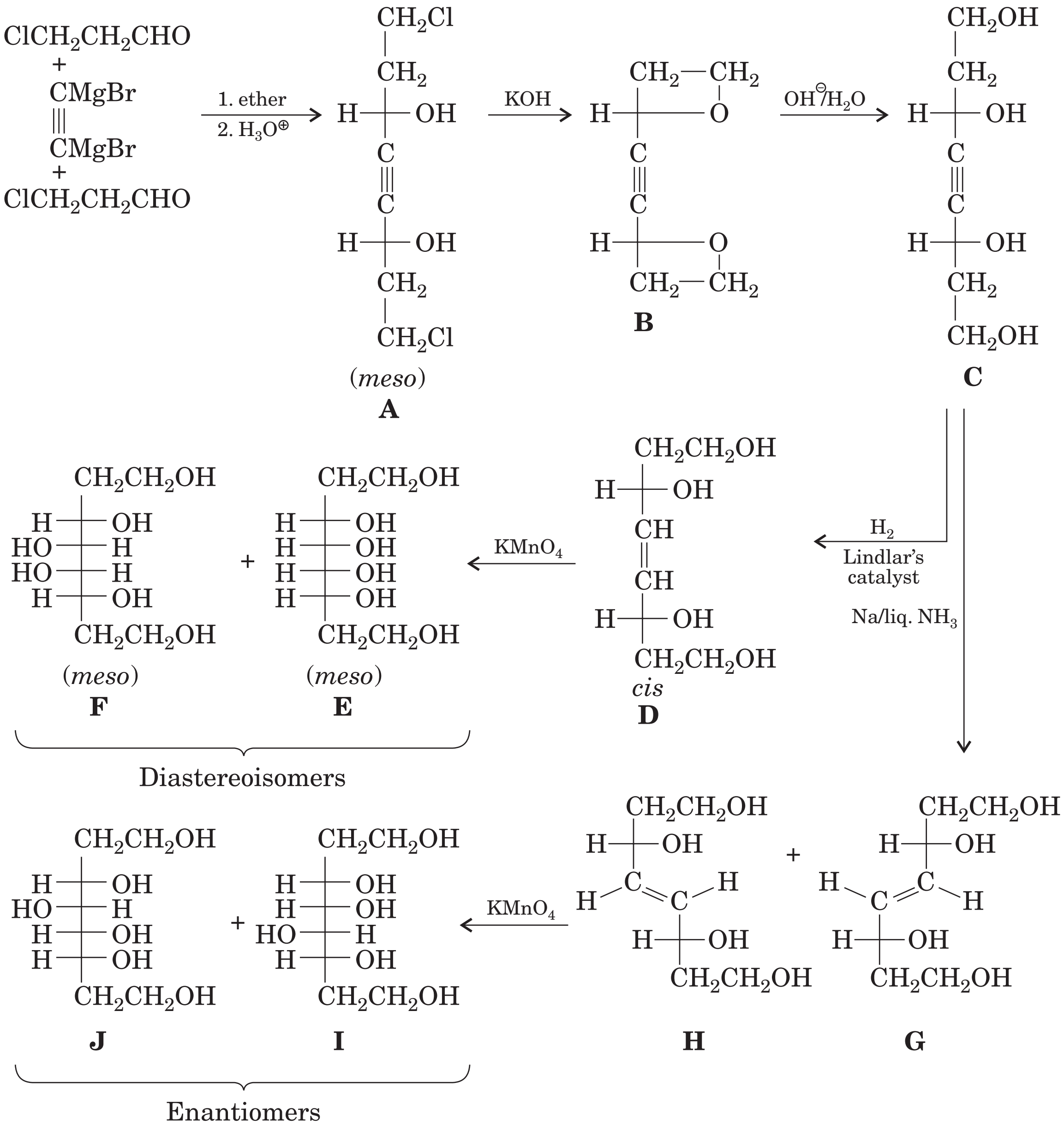
Now, HIO_4 oxidation of A produces one molecule of HCHO and two molecules of HCO_2H. Inspection of the structures shows that I, II and III, but not IV and V, can give the required products. Therefore, A is I or II or III.

37. Identify the compounds A—J in the following reaction sequence:



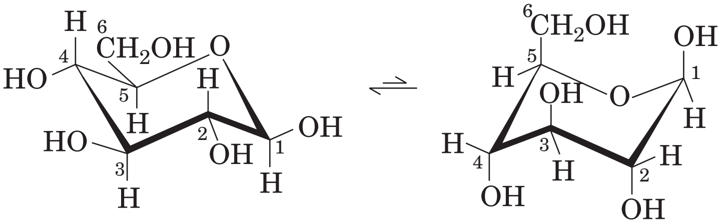
Indicate the stereochemical relationship between E and F and between I and J.

Solution



38. Draw the two chair conformations of β-D-glucopyranose. Which one of the two would you expect to represent the true conformation of β-D-glucose and why?

Solution The two chair conformations of β-D-glucopyranose can be drawn as follows:



I

(More stable because all substituents are equatorial)

II

(Less stable because all substituents are axial)

I is expected to represent the true conformation of β-D-glucose because it is much more stable than the conformation II.

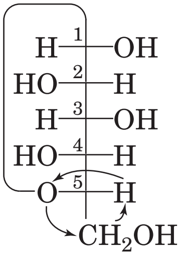
39. Draw a Fischer projection, a Haworth projection, and for the pyranoses, a chair conformation for each of the following sugars:

(a) β-L-(–)-Glucopyranose **(b) β-D-(+)-Fructofuranose**

(c) α-L-(+)-fructopyranose **(d) α-D-Ribofuranose**

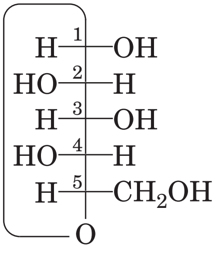
Solution

(a) β-L-(–)-Glucopyranose



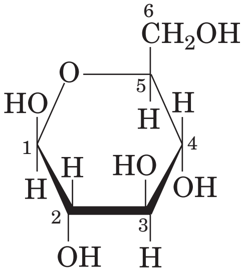
Fischer projection

$\xrightarrow{\text{Cyclic permutation}}$



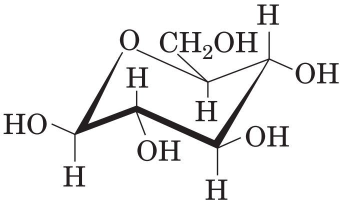
Modified Fischer projection

≡



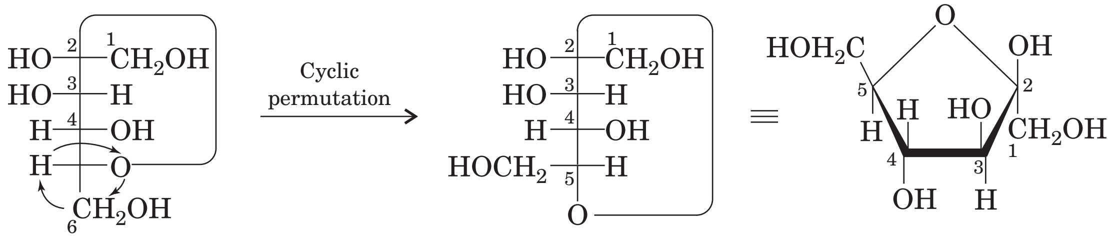
Haworth projection

≡



Chair conformation

(b) β-D-(+)-Fructofuranose

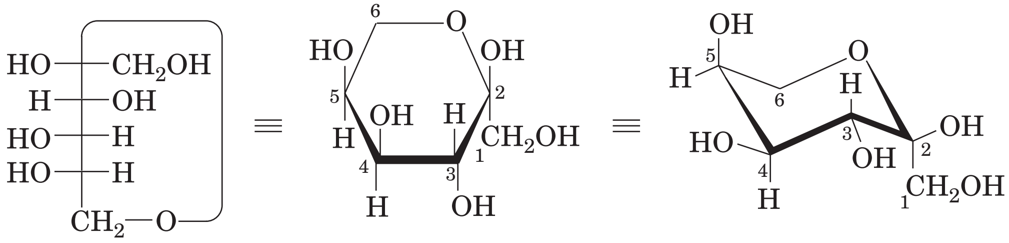


Fischer projection

Modified
Fischer projection

Haworth projection

(c) α-L-(+)-Fructopyranose

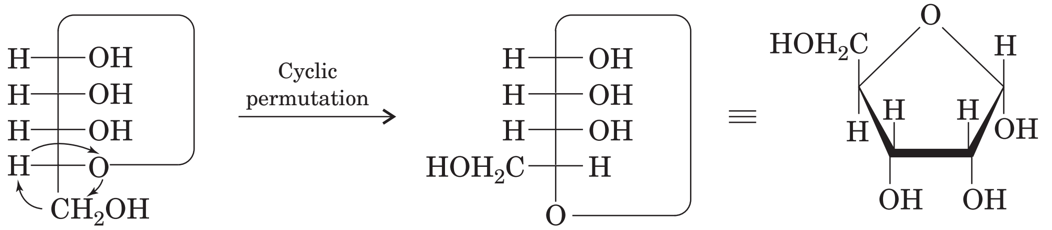


Fischer projection

Haworth projection

Chair conformation

(d) α-D-Ribofuranose



Fischer projection

Modified
Fischer projection

Haworth projection

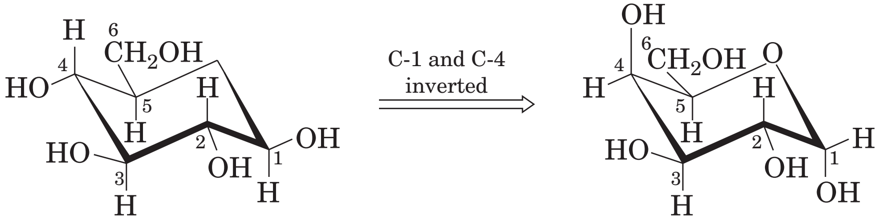
40. Draw the chair conformation of each of the following compounds from its relationship to β-D-glucopyranose:

(a) α-D-Galactopyranose **(b) β-L-Mannopyranose**

(c) β-D-Gulcopyranose **(d) α-D-Allopyranose**

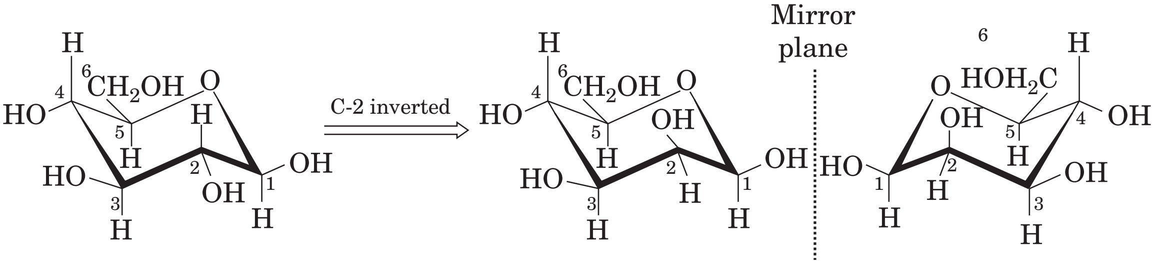
Solution It is known that all the –OH groups in β-D-glucopyranose are in equatorial positions. Therefore, it is easy to draw the chair conformation of any other aldehexose in its pyranose form.

(a) Since D-galactose is the C-4 epimer of D-glucose and the α-anomer differs from the β-anomer of C-1 (the anomeric carbon), the chair conformation of α-D-galactopyranose can be drawn by interchanging the positions of H and OH both at C-4 and C-1 of β-D-glucopranose.



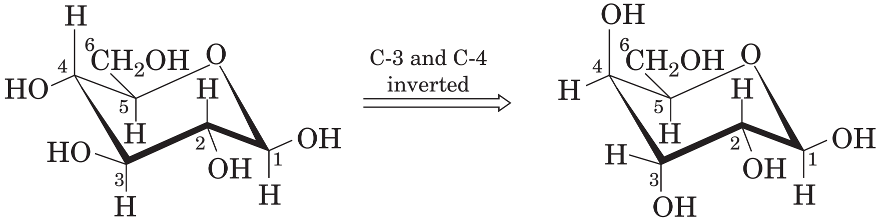
β-D-Glucopyranose α-D-Galactopyranose

(b) To draw an L-pyranose, the corresponding D-pyranose is to be drawn first, and then its mirror image is to be drawn. D-Mannose is the C-2 epimer of D-glucose. Therefore, the chair conformation of β-D-mannopyranose can be easily drawn by interchanging the positions of H and OH at C-2 of β-D-glucopyranose. Then, the mirror image of β-D-mannopyranone is drawn to get β-L-mannopyranose.



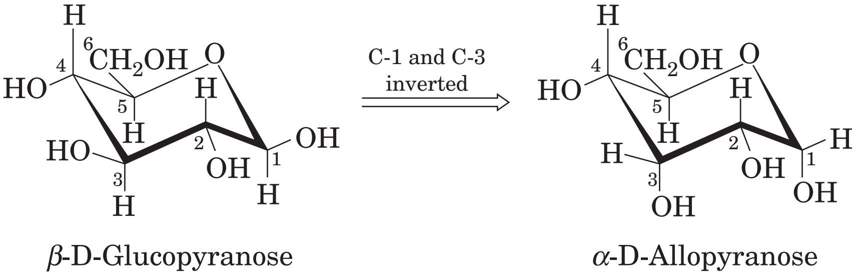
β-D-Glucopyranose β-D-Mannopyranose β-L-Mannopyranose

(c) Since D-gulose differs from D-glucose in C-3 and C-4 configurations, the chair form of β-D-gulopyranose can be drawn by interchanging the positions of H and OH both at C-3 and C-4 of β-D-glucopyranose.



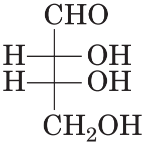
β-D-Glucopyranose β-D-Gulopyranose

(d) D-Allose in the C-3 epimer of D-glucose. Again, the α-anomer differs from the β-anomer at C-1 (the anomeric carbon). So, the chair form of α-D-allopyranose can be drawn by interchanging the positions of H and OH both at C-3 and C-1.



41. What is the smallest aldose also to form a cyclic hemiacetal? Give an example.

Solution A tetrose is the smallest aldose able to form a cyclic hemiacetal (a five-membered, i.e., a furanose ring). For example:

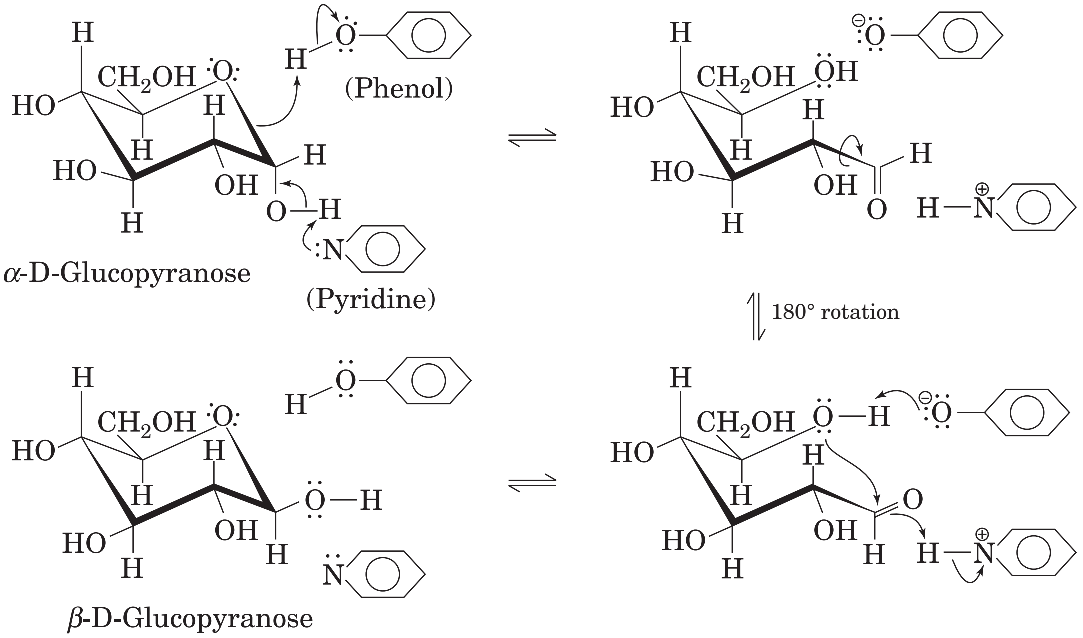


D-Erythrse

42. How it has been established that the solvent should have both acidic and basic properties for mutarotation to take place?

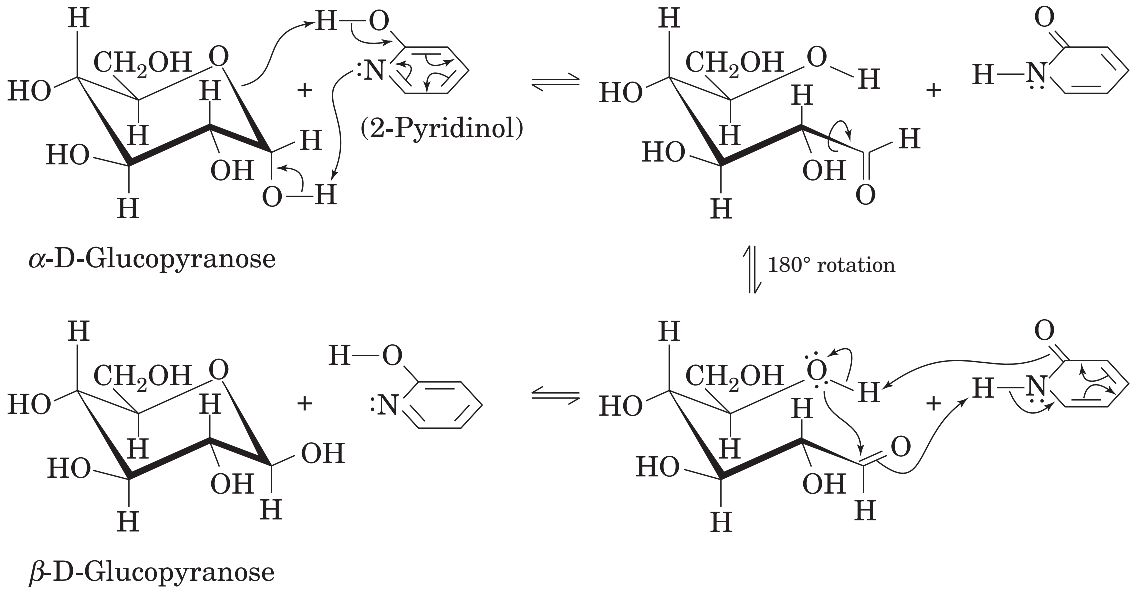
Solution It has been observed that mutarotation does not take place in either of the solvents, pyridine (a weak base) or a phenol (a weak acid), but takes place quite readily in a mixture of the two. This observation, therefore, suggests that the solvent should have both acidic and basic properties for mutarotation to take place.

The process of mutarotation in a mixture of pyridine and phenol may be shown as follows:



43. α-D-Glucopyranose undergoes mutarotation readily in the presence of 2-pyridinol. Explain.

Solution 2-Pyridinol can act as an acid-base catalyst. It can give $H^{\oplus}$ to the acetal oxygen and can remove $H^{\oplus}$ from the anomeric –OH in a synchronous manner and for this reason, α-D-glucopyranose undergoes ready mutarotation in the presence of 2-pyridinol.



44. The value of $[\alpha]_D$ of α-D-glucopyranose is +112°, while that of the β-anomer is +18.7°, when either of the pure anomers is dissolved in water, the specific rotation gradually changes to +52.7°. Calculate the percentages of the two anomers present at equilibrium.

Solution Let, the mole fraction of the α-anomer ($[\alpha]_D = +112°$) present at equilibrium is x and the mole fraction of the β-anomer ($[\alpha]_D = +18.7°$) is y. Since the observed rotation of the mixture is +52.7°, we have

$$x(+112°) + y(+18.7°) = +52.7° \qquad \text{(i)}$$

Since the amount of the open-chain form present at equilibrium is very small, the fraction present as the α- and β-anomer should account for all the glucose:

$$x + y = 1, \text{ or } y = 1 - x$$

Substitution $(1 - x)$ for y in the equation (i), we have,

$$x(112°) + (1 - x)(18.7°) = 52.7°$$

Solving this equation for x, we have $x = 0.36$ and $y = (1 - 0.36) = 0.64$. Therefore, the amounts of the α- and the β-anomer present at equilibrium are 36% and 64%, respectively.

45. Draw the two chair conformations of each of the following compounds and indicate the more and less stable conformers:

(a) α-D-Idopyranose

(b) α-D-Allopyranose

(c) α-D-Arabinopyranose

(d) α-D-Gulopyranose

(e) β-D-Xylopyranose

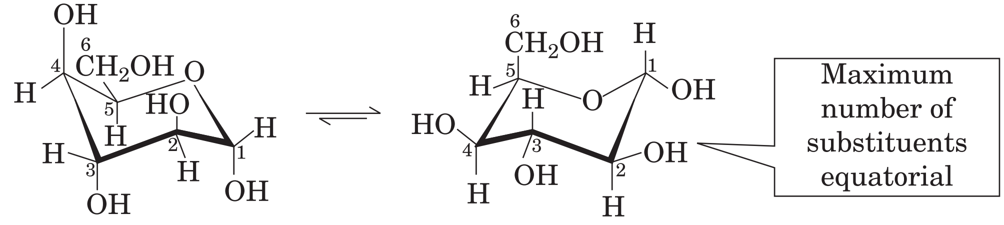
(f) β-D-Fructopyranose

(g) α-L-Glucopyranose

(h) β-D-Mannopyranose

Solution

(a)

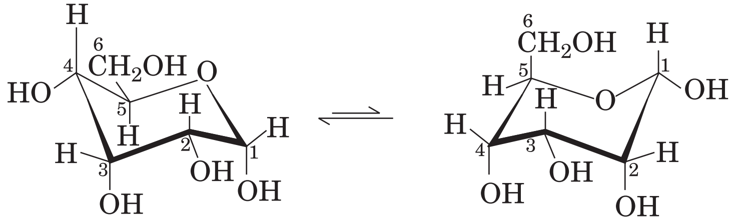


Maximum number of substituents equatorial

(less stable conformer) (more stable conformer)

α-D-Idopyranose

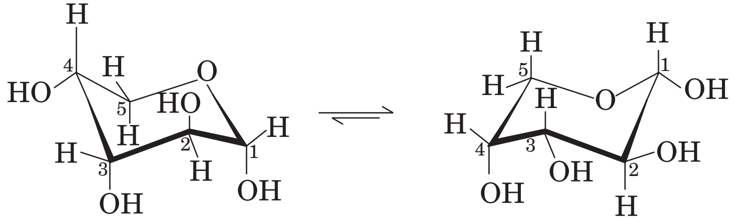
(b)



(more stable conformer) (less stable conformer)

α-D-Allopyranose

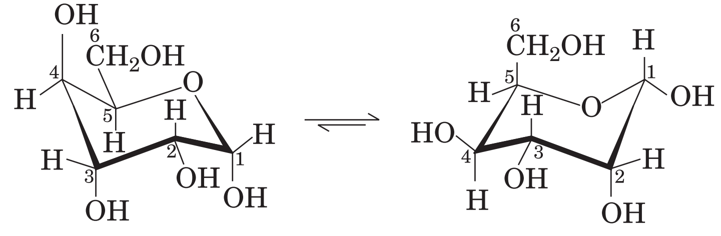
(c)



(less stable conformer) (more stable conformer)

α-D-Arabinopyranose

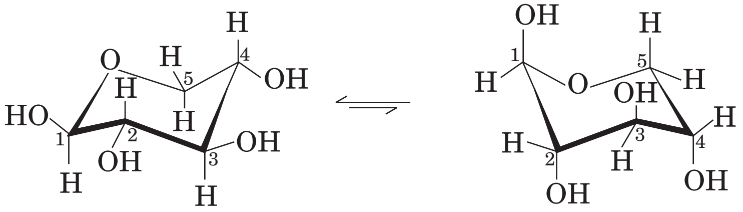
(d)



(less stable conformer) (more stable conformer)

α-D-Gulopyranose

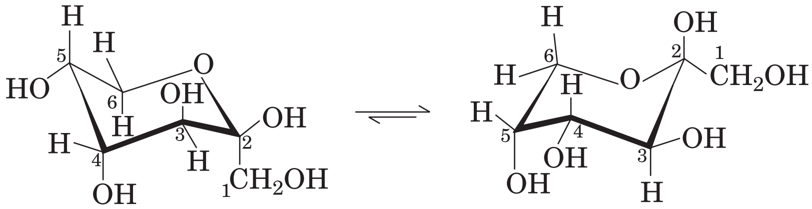
(e)



(more stable conformer) (less stable conformer)

β-L-Xylopyranose

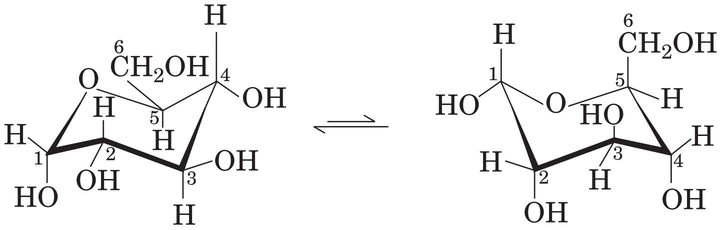
(f)



(less stable conformer) (more stable conformer)

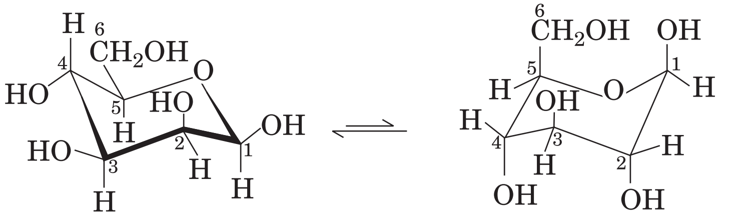
β-D-Fructopyranose

(g)



(more stable conformer) (less stable conformer)

(h)



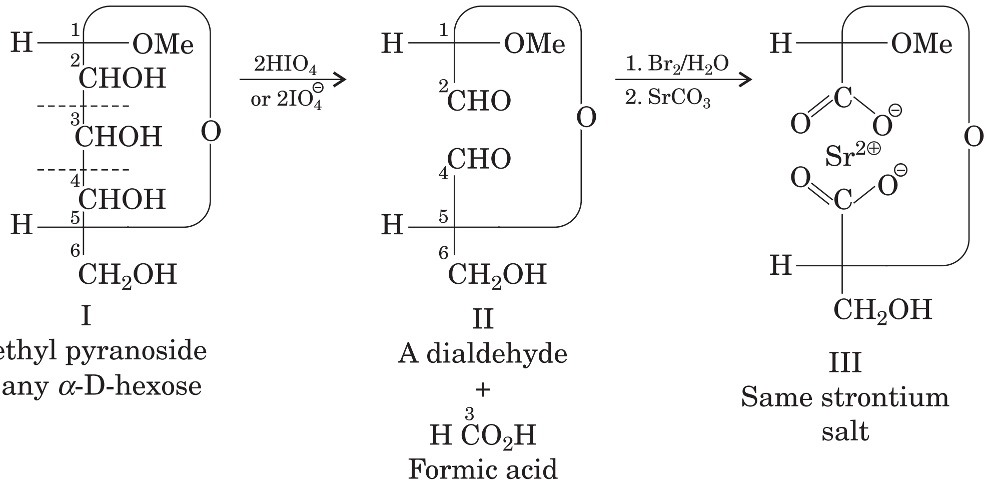
(more stable conformer) (less stable conformer)

β-D-Mannopyranose

It is to be noted that in general the more stable conformation is the one in which the bulkiest group, —CH_2OH, occupies an equatorial position. However, in an extreme case, to permit many –OH groups to take up equatorial positions, the —CH_2OH group may be forced into an axial position.

46. How would you establish that all methyl pyranosides of α-D-hexose series have the same configuration about C-1?

Solution Periodic acid oxidation of any methyl pyranoside (I) of α-D-hexose series produces formic acid and the same dialdehyde (II). Oxidation destroys the chirality centres at C-2, C-3 and C-4 (C-2 and C-4 are oxidized to —CHO groups and C-3 is eliminated as formic acid). The configuration is preserved about C-1 and C-5. Configuration about C-5 is the same for all members of the D family. The same products can then be obtained from all these glycosides only if they have the same configuration about C-1. This has further been proved by the fact that these dialdehydes can be converted into the same strontium salt (III). (That the C-1 –OH is on the right in the α-D hexose series has been established by X-ray analysis.)



I
Methyl pyranoside
of any α-D-hexose

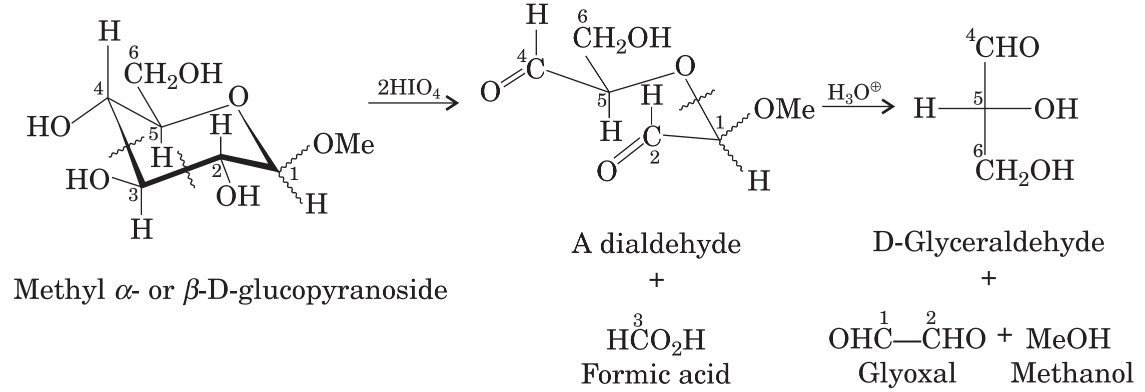
II
A dialdehyde
+
$H\overset{3}{C}O_2H$
Formic acid

III
Same strontium
salt

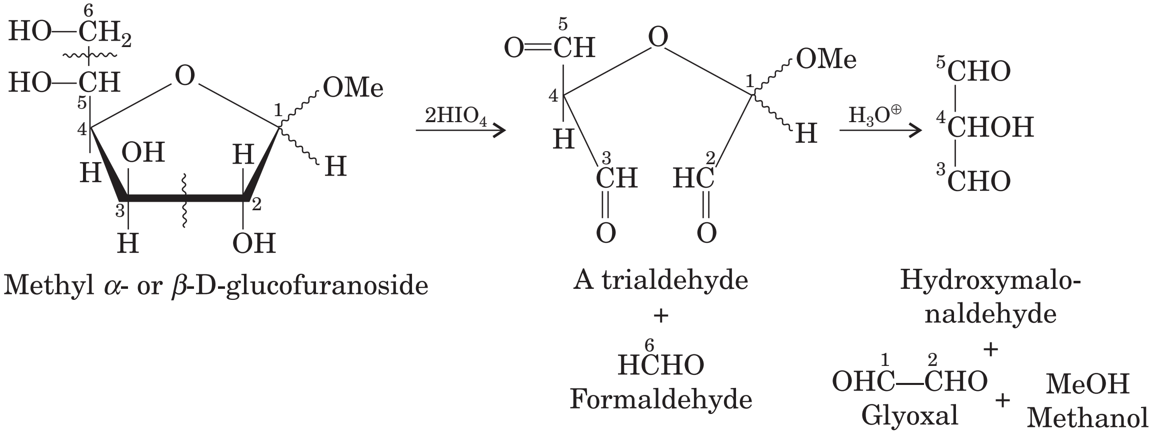
[The method which demonstrates that different glycosides of α-D-hexose series have the same configuration about C-1 and C-5 is known as the Jackson and Hudson's method.]

47. How would you prove that the methyl glycoside ($[\alpha]_D^{20°}$ = +159°) obtained by refluxing D-(+)-glucose in methanol solution in the presence of a little hydrochloric acid, is a six-membered ring and not a five-membered ring?

Solution When this methyl glucoside is allowed to react with HIO_4, it is observed that this glycoside consumes two molar equivalents HIO_4 and produces one molar equivalent of formic acid and one molar equivalent of a dialdehyde (which on hydrolysis produces D-glyceraldehyde, glyoxal and methaol). This observation, therefore, suggests that the glycoside is a six-membered ring, i.e., it is methyl α- or β-D-glycopyranoside.

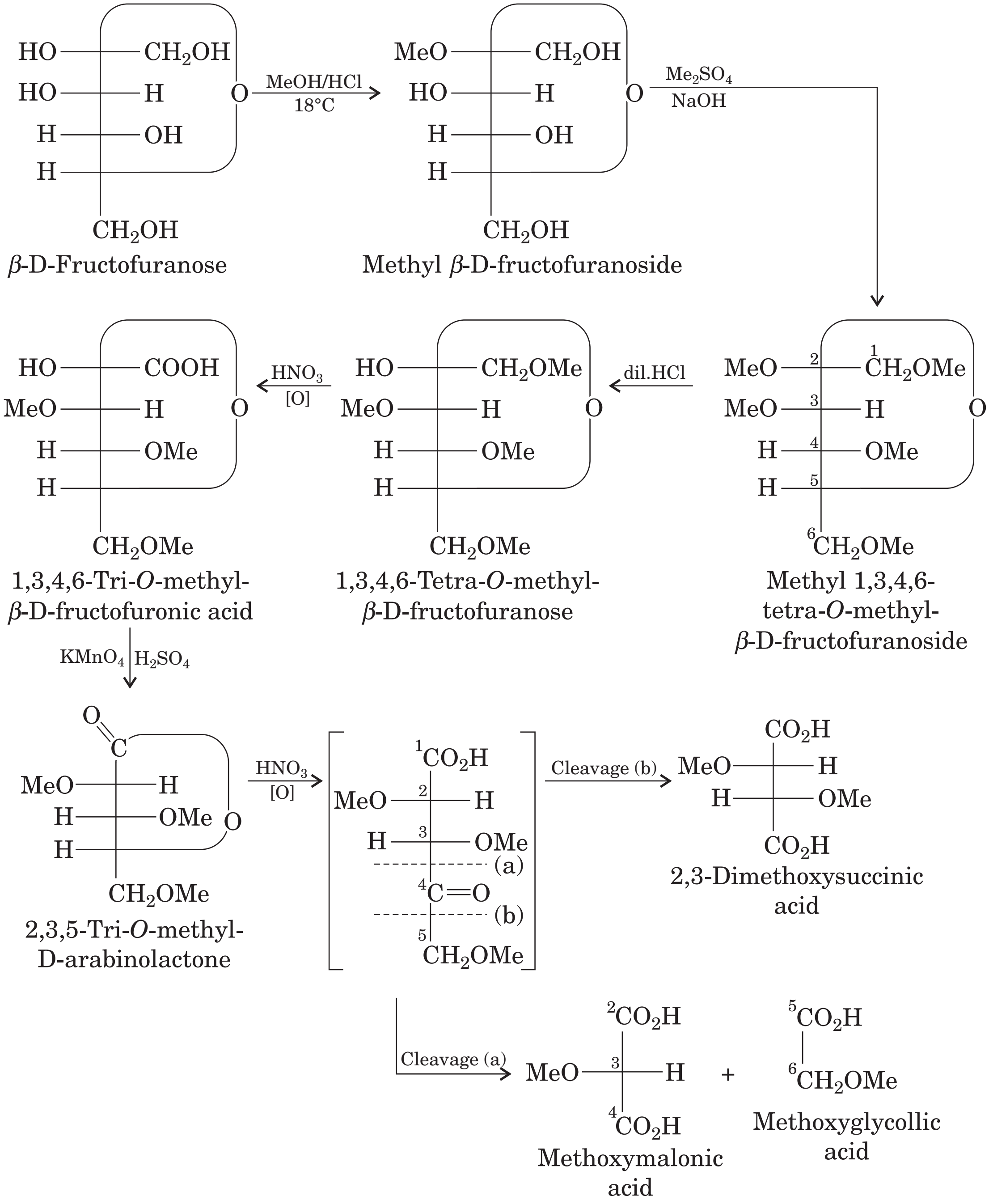


Were the ring five-membered (a furanose ring), two molar equivalents of HIO_4 would be required, but one molar equivalent of formaldehyde and one molar equivalent of a trialdehyde (which would yield hydroxymalonaldehyde, glyoxal and methanol on hydrolysis) would be formed.



48. What would have been the products obtained from the Howarth-Hirst procedure if (–)-fructose possesses a furanose ring structure?

Solution Methoxymalonic acid, methoxy glycollic acid and 2,3-dimethyloxysuccinic acid would have been obtained from the Haworth-Hirst procedure if D-(–)-fructose possesses a furanose (five-membered) ring structure. This may be shown by the following sequence of reactions.

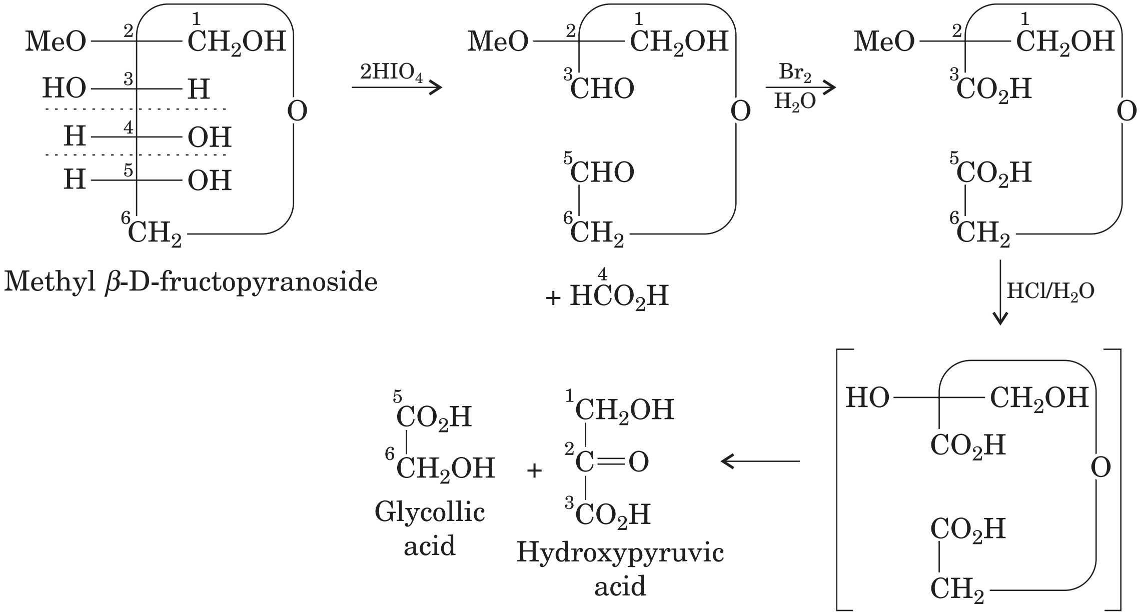

MeOH/HCl
18°C
Me2SO4
NaOH
β-D-Fructofuranose
Methyl β-D-fructofuranoside
dil.HCl
HNO3
[O]
Methyl 1,3,4,6-tetra-O-methyl-β-D-fructofuranoside
1,3,4,6-Tetra-O-methyl-β-D-fructofuranose
1,3,4,6-Tri-O-methyl-β-D-fructofuronic acid
KMnO4 H2SO4
2,3,5-Tri-O-methyl-D-arabinolactone
HNO3
[O]
(a)
(b)
Cleavage (b)
2,3-Dimethoxysuccinic acid
Cleavage (a)
Methoxymalonic acid
Methoxyglycollic acid

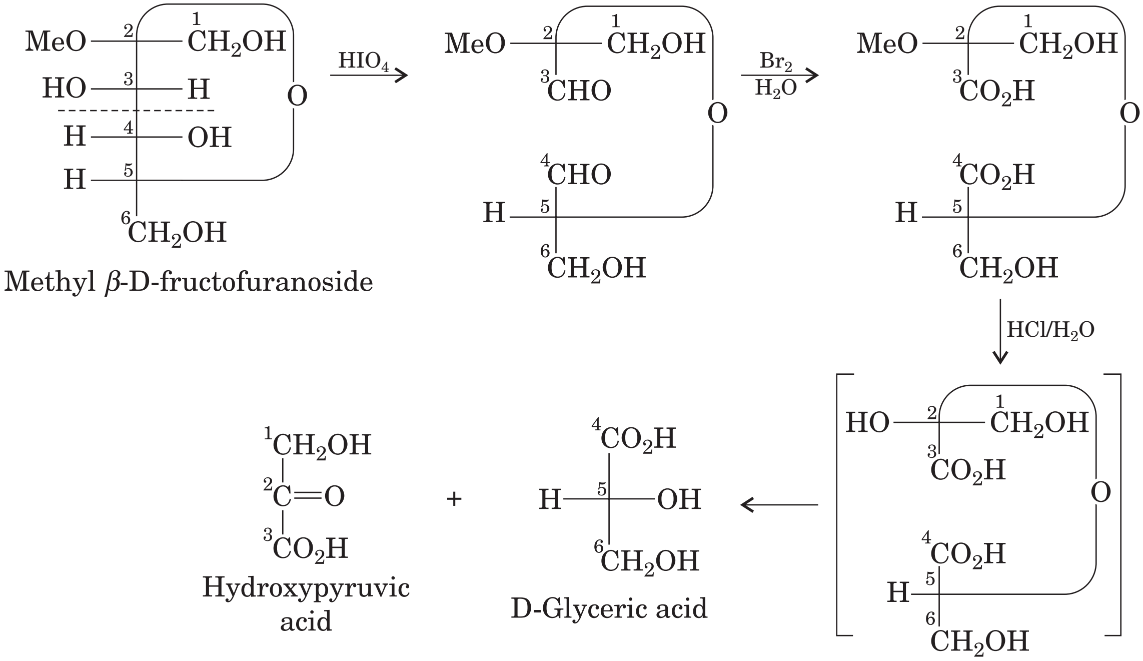
49. How can it be established by the following reaction sequence whether a methyl fructoside has a pyranose or furanose ring?

$$\text{Glycoside} \xrightarrow{HIO_4} \xrightarrow{Br_2/H_2O} \xrightarrow{H_3O^{\oplus}}$$

Solution Periodic acid causes oxidative cleavage of 1,2-diols. Aqueous bromide causes oxidation of a —CHO group to a —COOH group, and dilute acid causes hydrolysis of the acetal, thereby freeing the degradation units.

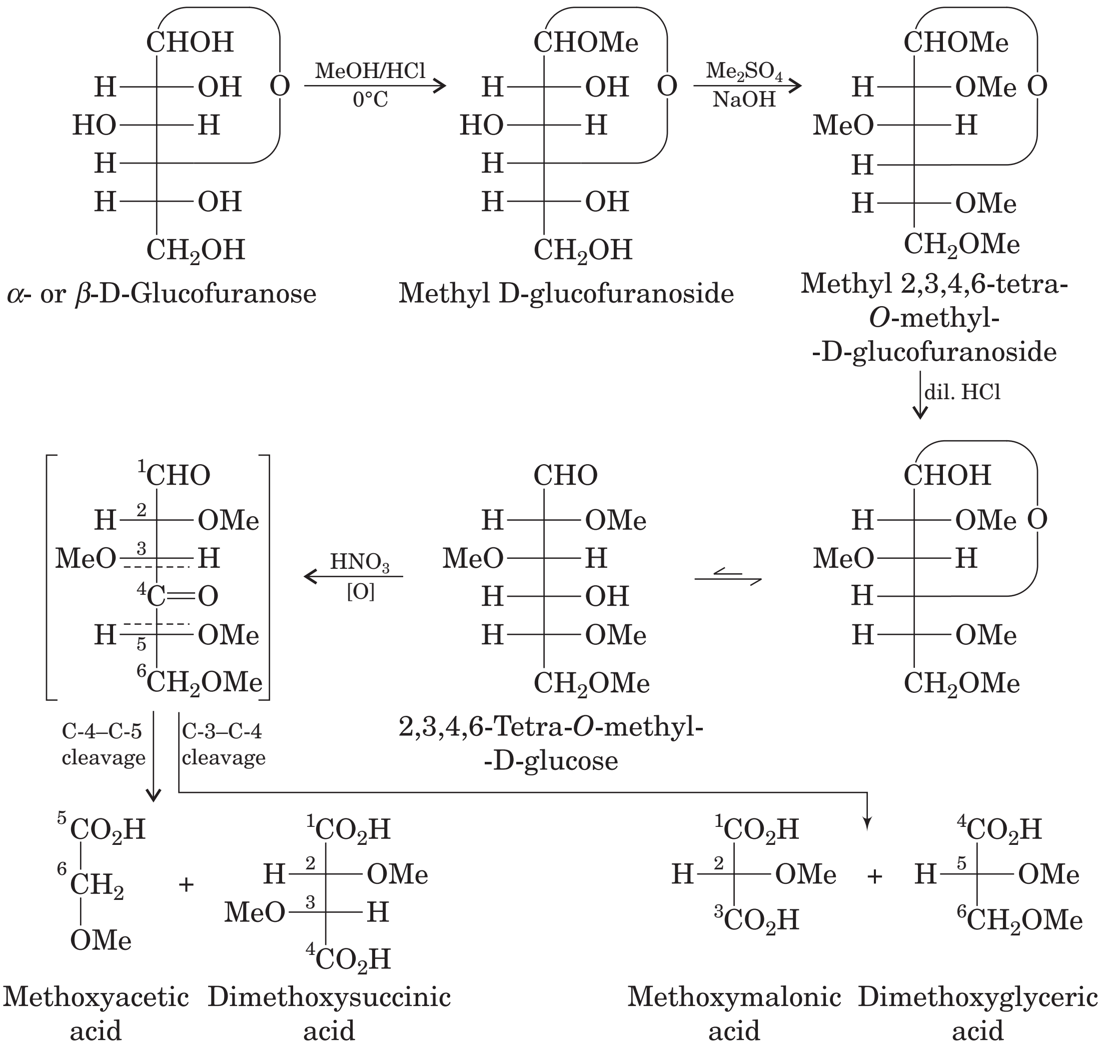
If methyl fructoside has a pyranose ring, formic acid (HCOOH), hydroxypyruvic acid and glycollic acid would have been obtained and if it has a furanose ring structure, hydroxypyruvic acid and glyceric acid would have been obtained.





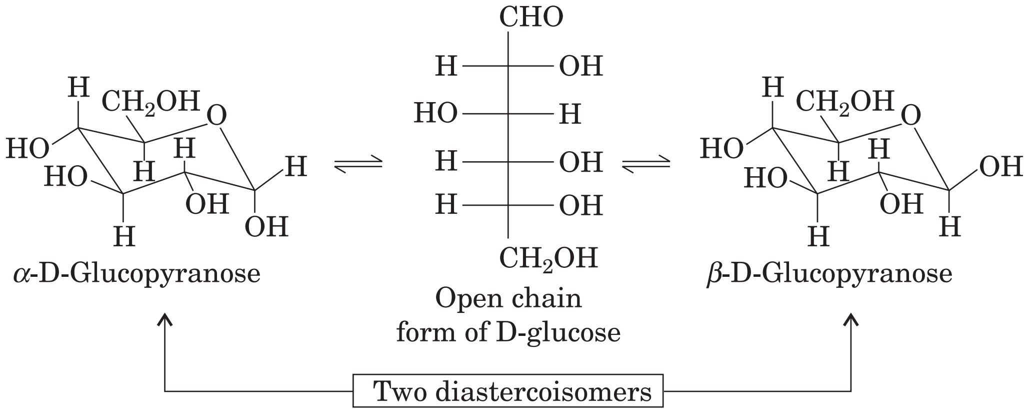
50. Predict the product expected to be obtained from the Haworth-Hirst procedure if D-(+)-glucose possesses a furanose ring structure?

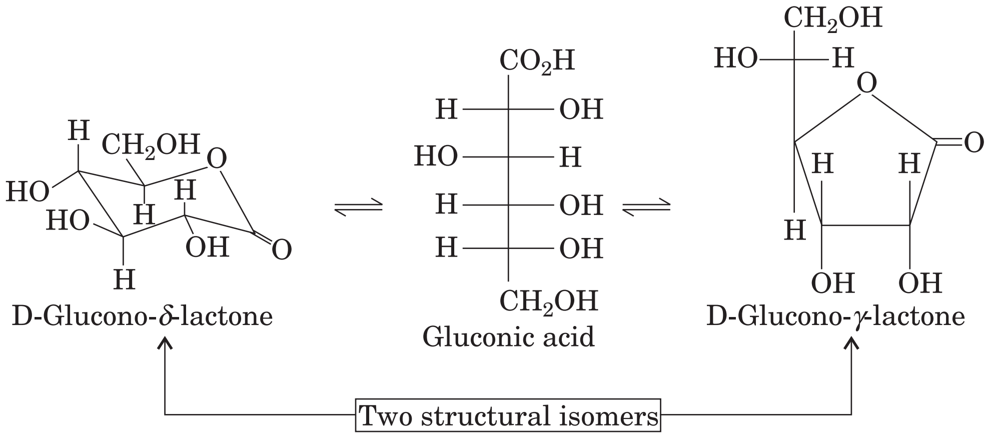
Solution



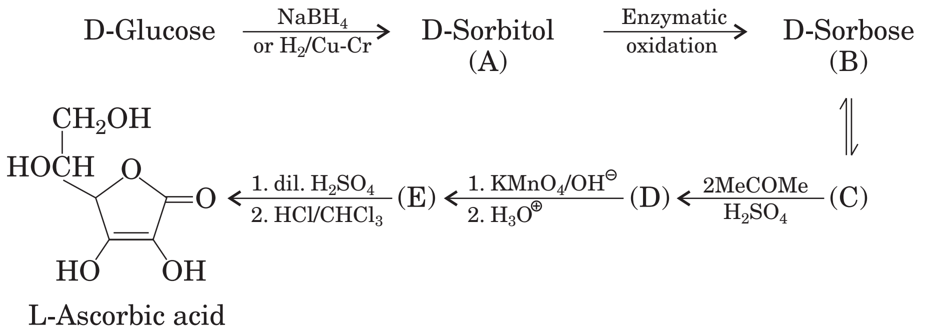
51. Mutarotations of α-D-glucose and δ-gluconolactone in water do not follow similar mechanism. Comment.

Solution Mutarotation of α-D-glucose is due to interconversion between two diastereoisomers (α- and β-anomers) involving hydrolysis and formation of hemiacetal (a nucleophilic addition to the carbonyl group). On the other hand, the mutarotation, of δ-gluconolactone is due to interconversion between two structural isomers (γ- and δ-lactones) involving hydrolysis and formation of lactone (nucleophilic acyl substitution).

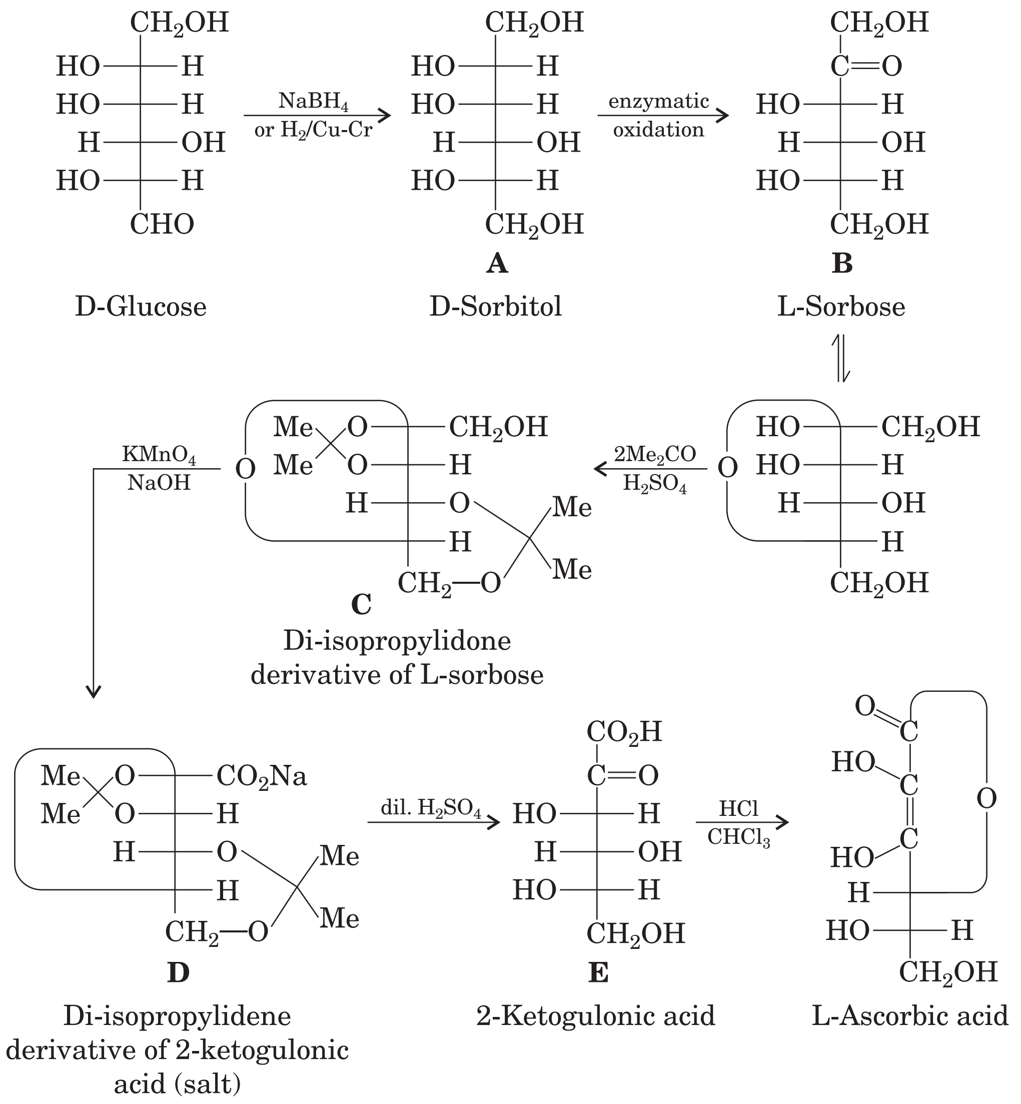




52. From the informations given below write the Fischer projection formulas of A, B, C, D and E.

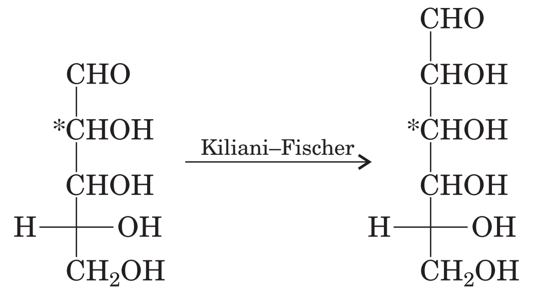


Solution The reaction sequence may be outlined as follows:



53. How would you prove that the –OH group on C-3 is on the left in the Fischer projection of D-(+)-glucose?

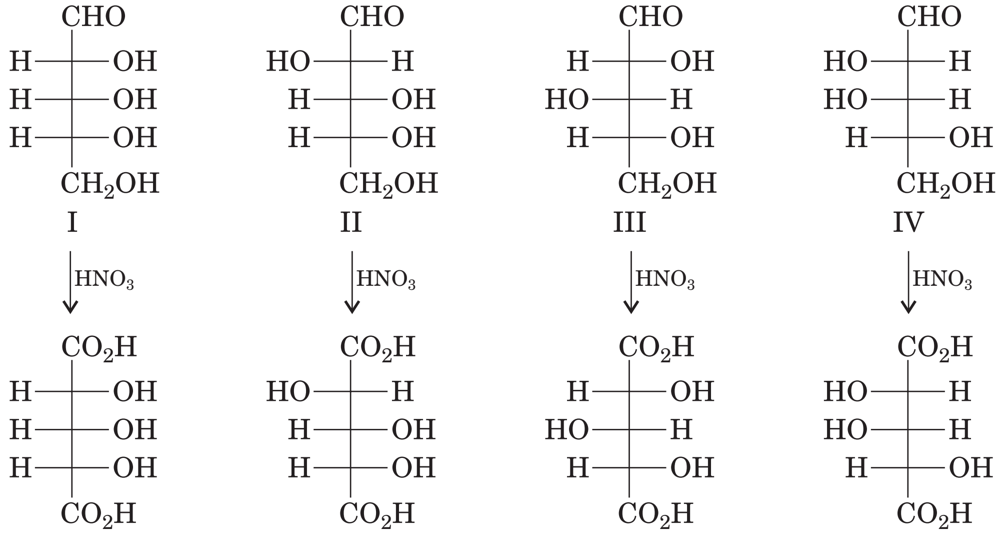
Solution D-(–)-Arabinose may be converted into D-(+)-glucose by the Kiliani–Fischer synthesis



D-(–)-Arabinose D-(+)-Glucose

[C-2 in arabinose is C-3 in glucose.]

When D-(–)-arabinose is oxidized with HNO_3, an optically active dicarboxylic acid is obtained. Of the four possible structures of D-(–)-arabinose ((I–IV) only two will give active dicarboxylic acid on oxidation.



Optically inactive Optically active Optically inactive Optically active

If (–)-arabinose has the configuration II or IV, it may be oxidized to yield an active diacid and for this to happen the –OH group on C-2 in (–)-arabinose must be on the left in the Fischer projection. Since C-2 in D-(–)-arabinone becomes C-3 in D-(+)-glucose, the –OH group on C-3 is on the left in Fischer projection of D-(+)-glucose.

STUDY PROBLEMS

1. Explain why most of the simple sugars are highly soluble in water.
2. Provide the IUPAC name, with *R* and *S* configurational designations for D-glucose.
3. α-D-Mannose has a specific rotation of +29.3°. The specific rotation of the β-anomer is –17.0°. Either of these anomers mutarotates in water to give a solution with

a specific rotation of +14.2°. Calculate the relative amounts of α and β anomers present at equilibrium.

4. Glucose is the most abundant aldohexose. Use a stereochemical analysis to speculate upon the reason for this observation.

5. It is the configuration of C-5 that makes D-glucose "D". However, inversion of configuration at C-5 does not convert D-glucose to L-glucose why? What is the result of such an inversion of configuration.

6. Identify the following sugars:
   (a) An aldohexose which yield the same phenylosazone as L-tagatose.
   (b) An aldopentose that is not D-arabinose yields D-arabinitol when reduced with $NaBH_4$.
   (c) A sugar that forms the same osazone as L-glucose with $PhNHNH_2$ but does not undergo oxidation by Br_2/H_2O.
   (d) A ketose which on reduction with H_2/Pd-C forms D-altritol and D-allitol.
   (e) An aldose which gives a *meso* aldaric acid on HNO_3 oxidation.

7. Which, if any, of the following are enantiomers?
   (a) α-D-Glucopyranose and β-L-glucopyranose
   (b) α-D-Fructopyranose and β-L-fructopyranose
   (c) α-D-Mannopyranose and α-L-mannopyranose
   (d) β-D-Fructopyranose and β-L-fructopyranose

8. Explain the difference between:
   (a) An anomer and an epimer (b) An epimer and a diastereoisomer (c) A D-sugar and an L-sugar (d) Mutarotation and racemization.

9. Draw the structures for and the name of the compounds which are related to β-D-glucopyranose as:
   (a) Enantiomer (b) Anomer
   (c) Epimer (d) Diastereoisomer

10. Explain the following observations:
   (a) α-D-Glucopyranose undergoes anomerization, whereas methyl α-D-glucopyranoside does not.
   (b) D-Glucose reacts with a 1 mole of methanol to form an acetal.
   (c) Mutarotation is catalyzed by hydroxypyridine but not by pyridine alone.
   (d) D-Talose contains a small fraction of β-pyranose form than D-glucose.
   (e) Acetals undergo hydrolysis more rapidly than ordinary ethers.
   (f) β-D-Glucopyranose reacts with EtOH/HCl is yield ethyl α-D-glucopyranoside predominantly.
   (g) The diacetal obtained when glucose is allowed to react with acetone has a furanose rather than a pyranose structure.
   (h) The reaction of PhCHO with D-glucose leads to the formation of 2,4-acetal preferentially.

(i) When *tert*-butyl β-D-glucopyranoside is hydrolyzed in $H_2{}^{18}O$, *tert*-butyl-oxygen cleavage is observed.

(j) The aldaric acids of D- and L-mannose are related as enantiomers.

(k) Epimeric sugars are produced in unequal amounts in Kiliani–Fischer synthesis.

(l) Osazone formation does not proceed beyond the first two carbon atoms.

11. Why would you not expect the anomers of an aldohexose to have specific rotation of equal magnitude but of opposite sign?

12. Why do aldoses react with Fehling's solution and $PhNHNH_2$, but not with $NaHSO_3$? [**Hint:** These are typical reactions for the —CHO group. Therefore, the open chain aldehyde form remains in equilibrium with the cyclic hemiacetal forms. Since Fehling's and osazone reactions are irreversible, the equilibrium shifts to restore the low concentration of the aldehyde as it is depleted through reaction, and ultimately all the aldose react. The bisulphite addition, on the other hand, is reversible and enough aldehyde remains in equilibrium with the bisulphite addition product to satisfy the equilibrium with the anomeric forms. As a consequence, no noticeable reaction occurs.]

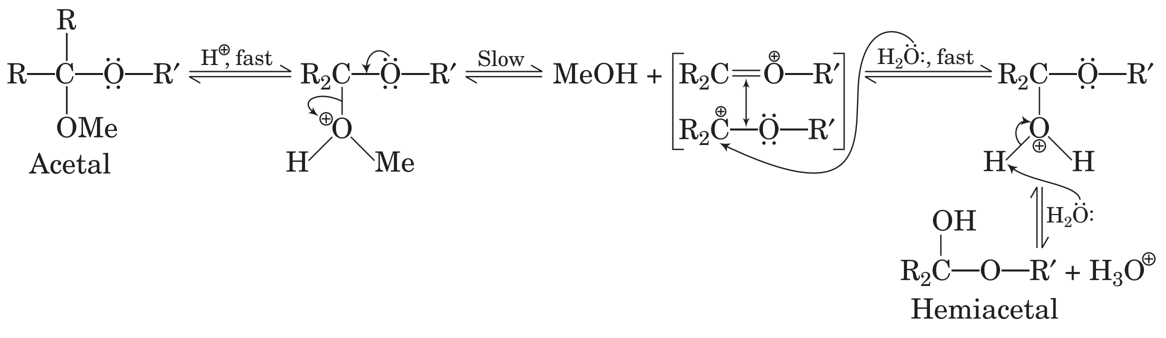
13. Determine whether D-glucose possesses a furanose or pyranose ring structure from the final products in the following reaction sequence:

$$\text{D-Glucose} \xrightarrow{\text{MeOH/HCl}} \text{A} \xrightarrow[\text{NaOH}]{Me_2SO_4} \text{B} \xrightarrow{\text{dil. HCl}} \text{C} \xrightarrow[\text{[O]}]{HNO_3} \begin{array}{c}\text{2,3-Dimethoxysuccinic}\\ \text{acid}\end{array} + \begin{array}{c}\text{2,3,4-Trimethoxyglutaric}\\ \text{acid}\end{array}$$

[**Hint:** If the ring is five-membered (furanose), 2,3-dimethoxysuccinic acid, dimethoxy glyceric acid and methoxyethanoic acid are expected to be obtained finally.]

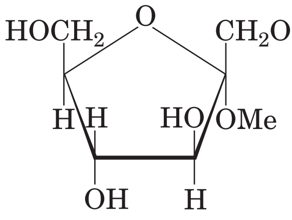
14. Draw the more stable chair conformation of α-D-fructopyranose. How does it differ from the β-D-fructopyranose?

15. The general mechanism for the first stage of acid-catalyzed acetal hydrolysis is as follows:

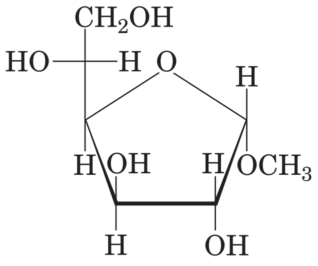


Basing on the above general mechanism suggest a reasonable explanation for each of the following observations:

(a) Methyl α-D-fructofuranoside (I) undergoes acid-catalyzed hydrolysis some 10^5 times faster than methyl α-D-glucofuranoside (II).

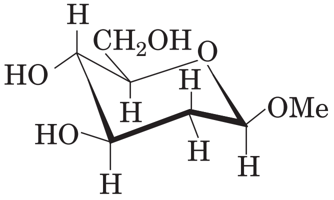


I

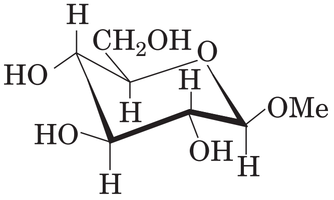


II

(b) The β-methyl glucopyranoside of 2-deoxy-D-glucose (III) undergoes hydrolysis several thousand times faster than that of D-glucose (IV).

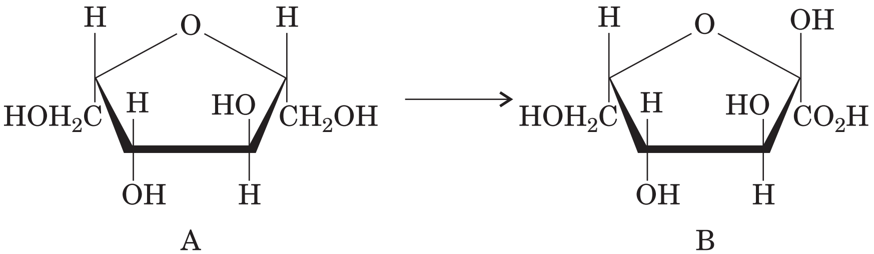


III

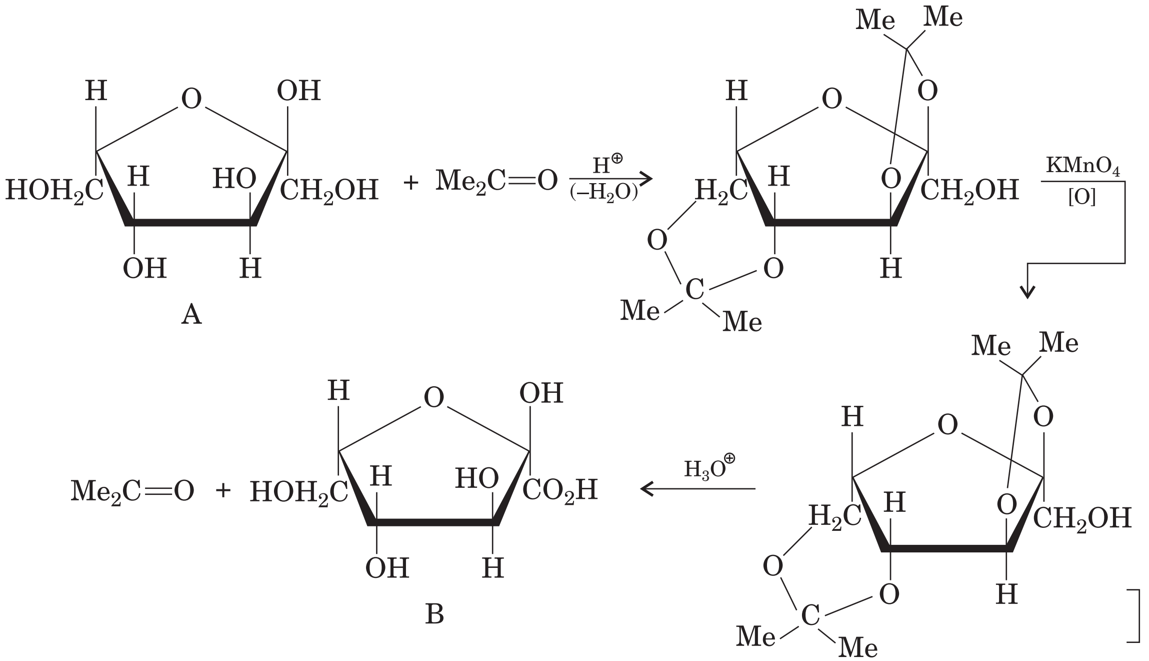


IV

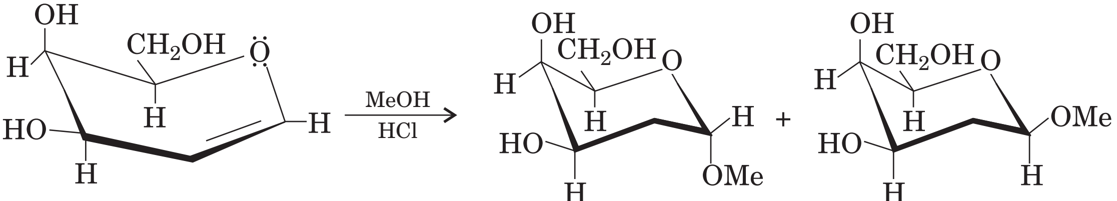
16. How would you carry out the following transformation?



[**Hint:** This may be carried out by protecting two pairs of adjacent –OH groups by forming isopropylidene or acetonide derivative by allowing the sugar to react with acetone in the presence of acid catalyst followed by oxidation and hydrolysis.



17. Methyl glycosides of 2-doxy sugars may be prepared by the acid-catalyzed addition of MeOH to unsaturated carbohydrates known as *glycals*.



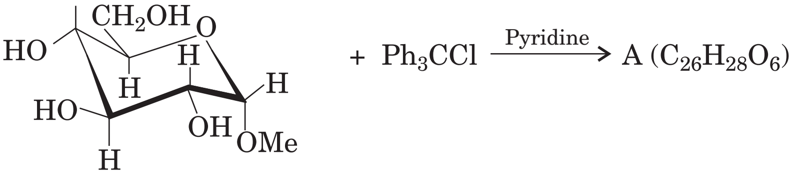
D-Galactal

Methyl 2-deoxy-α-D-lyxopyranoside

Methyl 2-deoxy-β-D-lyxopyranoside

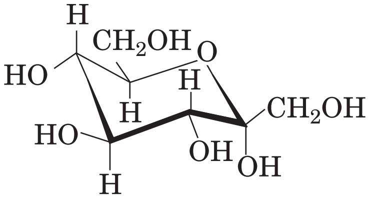
Suggest a reasonable mechanism for this reaction.

18. Predict the product (A) of the following reaction and explain its formation:

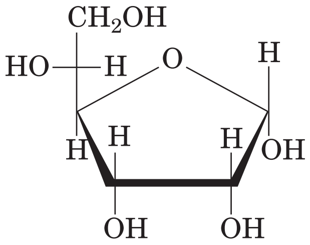


19. Write down the Fischer projection of the open-chain form of each of the following sugars:

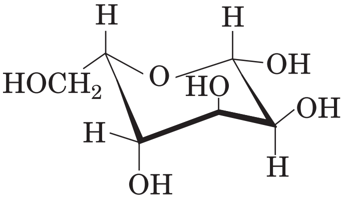
(a)



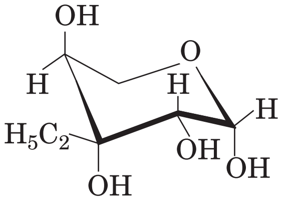
(b)



(c)



(d)



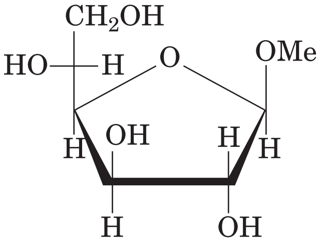
20. Give the products of HIO_4 oxidation of each of the following compounds. How many moles of the reagent is consumed per mole of substrate in each case?

(a) L-Ribose

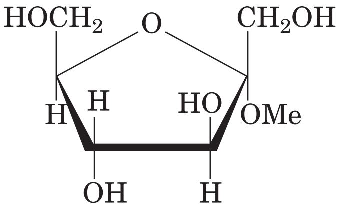
(b) D-Xylose

(c) Methyl α-D-glucopyranoside

(d)



(e)



21. On the basis of your knowledge of steric effects in six-membered rings, predict the preferred form (α- or β-pyranose) at equilibrium in aqueous solution for each of the following:

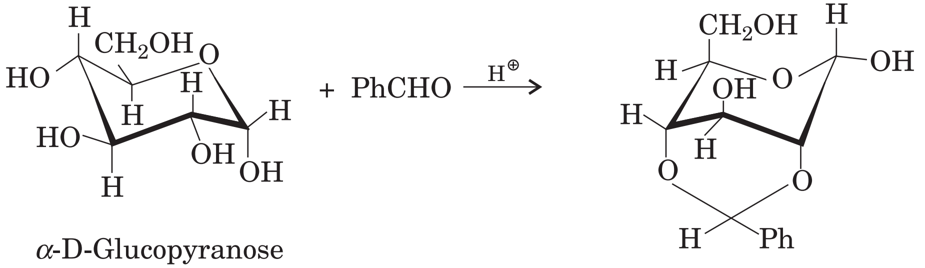
(a) L-Xylose

(b) D-Gulcose

(c) L-Talose

(d) D-Lyxose

22. Under proper reaction conditions D-glucose reacts with PhCHO in the presence of acid catalyst to give 2,4-*O*-benzylidene-D-glucose.



α-D-Glucopyranose

2,4-*O*-Benzylidene-D-glucose

This compound is reduced to 2,4-*O*-benzylidene-D-glucitol, which, when treated with HIO_4, the benzylidene derivative of an aldopentose is obtained. Hydrolysis of the latter compound yields the aldopentose. Write down the structure and name of the aldopentose.

23. Outline chemical tests that will distinguish between each of the following:
(a) L-Glucose and L-fructose
(b) D-Mannose and methyl β-D-mannopyranoside
(c) Methyl α-D-arabinofuranoside and methyl α-D-mannopyranoside
(d) L-2-Deoxyglucose and L-3-deoxyglucose
(e) Methyl β-D-ribofuranoside and methyl 2-deoxy-β-D-ribofuranoside

24. Give stereochemical formulas for the products A through D, and identify the final products:

$$\begin{tikzcd}
 & \underset{meso}{\text{C}} & \\
\text{A} \arrow[ur, "\text{KMnO}_4"] \arrow[dr, "\text{1. H COOOH}", "\text{2. H}_3\text{O}^{\oplus}"'] & \text{2-Butyn-1,4-diol} \arrow[l, "\text{H}_2"', "\text{Linlar's cat.}"] \arrow[r, "\text{Na}", "\text{Liq. NH}_3"'] & \text{B} \arrow[ul, "\text{1. HCOOOH}"', "\text{2. H}_3\text{O}^{\oplus}"] \arrow[dl, "\text{KMnO}_4"'] \\
 & \underset{\text{(racemic)}}{\text{D}} &
\end{tikzcd}$$

25. 'X' is a reducing hexose ($C_6H_{12}O_6$) which gives D-glucitol (D-sorbitol) upon reduction with sodium borohydride ($NaBH_4$), but when treated with phenylhydrazine ($PhNHNH_2$) it yields an osazone different from that of D-glucose. Identify the hexose 'X'.
[**Hint:** 'X' is L-gulose.]

26. Two L-aldohexoses, other than L-glucose, yield the same six-carbon aldaric acids when oxidized. Degradation of these aldohexoses to the corresponding aldopentoses followed by oxidation give two different five-carbon aldaric acids, one of which is optically active and the other is optically inactive. Both of the aldohexoses may be converted into their methyl glycopyranosides which, when oxidized with HIO_4, give the same compound as that obtained by similar treatment of D-glucose. Write down the Fischer projections of these two aldohexoses and trace the above reactions.
[**Hint:** The two aldohexoses are D-altrose and D-talose.]

27. Suggest chemical reactions to prove the simultaneous existence of pyranose, furanose and open-chain structures of D-glucose in aqueous solution.

28. Explain the formation of a diacetal when D-glucose is treated with $Me_2C{=}O$ under acidic conditions. Show how this reaction can be used for selective methylation of C-3 –OH group of D-glucose.

29. "Dilute acid hydrolysis of D-glucose-1-phosphate differs from ordinary alkyl esters in two ways; it is abnormally fast and takes place with cleavage of C—O bond" give reasons.

[**Hint:** α-D-Glucopyranosyl phosphate undergoes ready hydrolysis in dilute acid involving cleavage of the C-1—O bond and this is because the $—O(P{=}O)(OH)_2$ group is a better leaving group and the resulting carbocation is stabilized by resonance. On the other hand, ordinary alkyl esters (RCOOR′) undergoes hydrolysis in dilute acid involving acyl-oxygen bond cleavage. The process is relatively slow because it proceeds through a tetrahedral intermediate.]

30. Diisopropylidene derivative of D-glucose but not that of D-galactose can be alkylated at C-3 position. Give reason.

31. Explain the fact that in dry methanol there is 50% of α-D-(+)-glucopyranose.

32. An aldopentose [P] can be oxidized with dil. HNO_3 to an optically active aldaric acid. A Kiliani–Fischer synthesis starting with [P] gives two new aldoses [Q] and [R]. The aldose [Q] can be oxidized to an optically inactive aldaric acid, but the aldose [R] is oxidized to an optically active aldaric acid. Assuming the D-configuration, give the structures of [P], [Q] and [R] and also justify the assignments.

33. Discuss the validity of the following statements:

(a) Glucose is the only aldose that mutarotate.

(b) Glycosides mutarotate.

(c) There is a relationship between the ability of a sugar to mutarotate and to reduce Fehling's reagent.

(d) D-Mannose and D-galactose are epimeric hexoses.

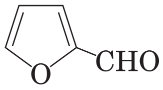
(e) α-D-Glucopyranoside is the mirror image of β-L-glucopyranoside.

(f) The periodic acid oxidation of D-mannose is faster than that of D-glucose.

34. What happens to an aldopentose when warmed with dilute acid? Give the mechanism of the reaction involved.

[**Hint:** $HOCH_2(CHOH)_3CHO \xrightarrow{\text{dil. } H_2SO_4}$

An aldopentose



Furfural]

35. How can you distinguish an aldohexose from a ketohexose through HIO_4 oxidation?

36. When the C-4 epimer of D-glucose is treated with $NaBH_4$, the product is optically inactive. Explain this loss of optical activity.

37. Show the steps and name the reaction for the overall process:

$$\text{D-Glucose} \xrightarrow[\text{AcOH}]{PhNHNH_2} X \xrightarrow{PhCHO} Y \xrightarrow{Zn/ACOH} Z$$

38. Supply structures A through D:

$$\text{D-Glucose} \xrightarrow[\text{base}]{NH_2OH} A \xrightarrow[\text{NaOAc}]{Ac_2O} B \xrightarrow{-AcOH} C \xrightarrow[\text{MeOH}]{\text{NaOMe}} D$$

[**Hint:** Step-down of the sugar chain by the Wohl degradation.]

39. How would you carry out the following transformations?

(a) Methyl D-glucopyranoside → Methyl D-glucofuranoside

(b) D-Glucose → $AcOCH_2(CHOAc)_4\ CH_2OH$ (Aldehydo-D-glucose pentaacetate)

(c) D-Allose → $CH_3(CHOH)_4CH_2OH$

(d) D-Arabinose → D-Fructose

(e) D-Glucose → 3-Deoxy-D-glucose

40. Explain the formation of a diacetal when D-glucose is treated with acetone under acidic condition. Show how this reaction can be used to selective methylation of C-3 –OH group of D-glucose.

41. Why D-glucose is called dextrose, but D-fructose is called levulose?

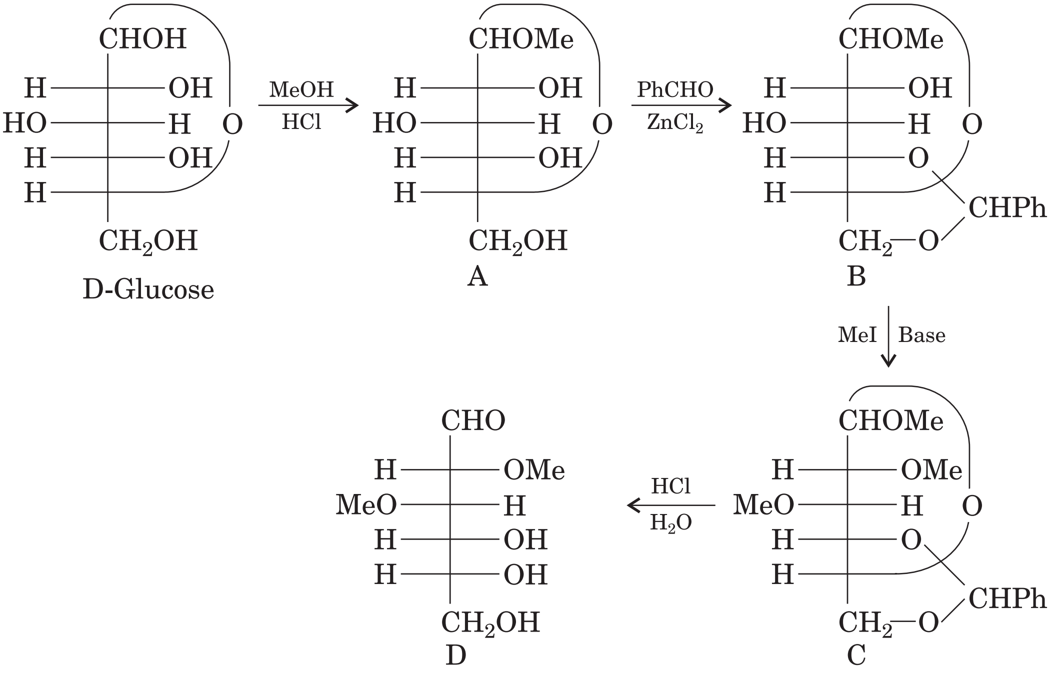
42. Identify the optically active compound $A(C_6H_{12}O_6)$ which reduces Fehling's solution and responds to the following reactions:

$$\begin{tikzcd} A \arrow[r, "HCN"] \arrow[d, dash] & {} \arrow[r, "\text{hydrol.}"] & {} \arrow[r, "HI/P", "\Delta"'] & \text{2-Methylhexanoice acid} \\ {} \arrow[r, "PhNHNH_2(Xs)", "AcOH"'] & \text{D-Glucosazone} \end{tikzcd}$$

43. Give the structures of the products A–D and rationalize their formation:

$$\text{D-Glucose} \xrightarrow[\text{HCl}]{\text{MeOH}} A \xrightarrow[ZnCl_2]{\text{PhCHO}} B \xrightarrow[\text{base}]{\text{MeI}} C \xrightarrow[H_2O]{\text{HCl}} D$$

[**Hint:**



44. Compare the rate of bromine-water oxidation of α-D-glucopyranose and β-D-glucopyranose.

45. What is the pre-condition for the formation of cyclic ketal with acetone in H_2SO_4 for a D-hexose?
[**Hint:** Acetone condenses with *cis*-hydroxyl groups on adjacent carbon atoms.]

46. Draw the more stable chair conformation for each of the following:

(a) α-D-Arabinopyranose	(b) β-D-Allopyranose
(c) β-L-Glucopyranose	(d) β-D-Glucopyranose
(e) β-D-Xylopyranose	(f) β-D-Fructopyranose

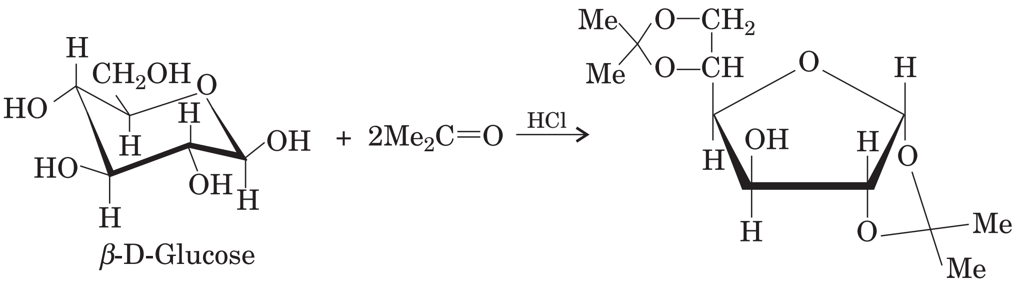
47. The methyl glycoside A on HIO_4 oxidation yields the same product as that obtained from methyl α-glycosides of the D-aldohexoses. However, it consumes only one mole of HIO_4 and yields no formic acid.
(a) How many carbon atoms are there in A and what is the ring size? When A is methylated, hydrolyzed, and then vigorously oxidized by HNO_3, the dicarboxylic acid obtained is the di-*O*-methyl ether of (–)-tartaric acid. Predict the complete structure and the configuration of the glycoside A.

48. What do you mean by the term 'anomeric effect'? Give plausible explanation for anomeric effect.

49. (a) Explain why D-fructose reduces Fehling's solution although it is a ketohexose.
(b) D-Glucose reacts with Ac_2O to give two isomeric pentaacetates neither of which reduces Fehling's or Tollens' reagent. Account for these observations.

50. When any of D-glucose, D-fructose or D-mannose is separately treated with alkali, we get a mixture of three monosaccharides. Identify them and give the necessary mechanism to explain this fact.

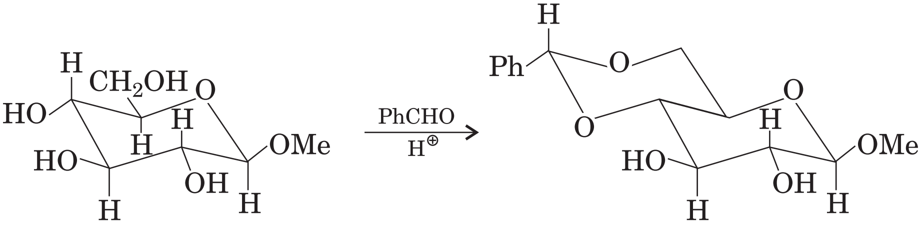
51. When D-(+)-glucose is treated with $Me_2C{=}O$ under acidic conditions, a diacetal of the furanose form of glucose forms slowly. Explain why the diacetal has a furanose rather than the usual pyranose ring structure.



β-D-Glucose

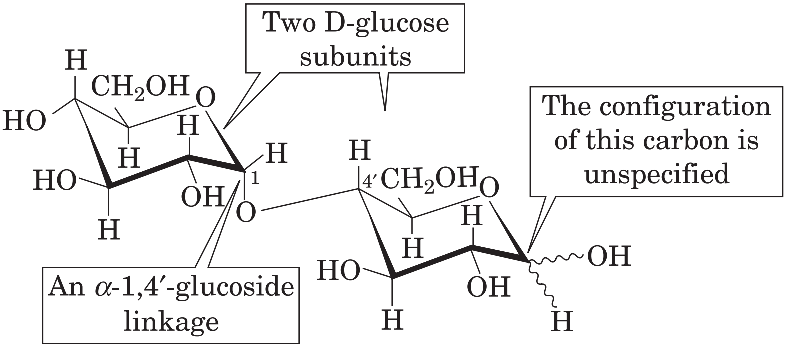
A di-*O*-isopropylidene-α-D-glucofuranose

52. Draw a stepwise mechanism for the following reaction:



9.3 DISACCHARIDES

When the hemiacetal group of a monosaccharide molecule forms an acetal by reacting with an –OH group (anomeric or other) of another monosaccharide molecule, a glycoside is formed. This is what is called a *disaccharide*. Disaccharides are, therefore, compounds with two monosaccharide subunits hooked together by an acetal linkage. Maltose, for example, is a disaccharide obtained from the hydrolysis of starch. It consists of two D-glucose subunits hooked together by an α-1,4′-glycosidic linkage (the linkage between C-1 of one sugar subunit and C-4 of the other). That C-4 is not in the same ring as C-1 is indicated by the 'prime' superscript. Since the oxygen atom involved in the glycosidic linkage is in the α-position (axial when a sugar is shown in a chair conformation), the linkage is an α-1,4′-glycosidic linkage.


Two D-glucose subunits
The configuration of this carbon is unspecified
An α-1,4′-glucoside linkage
H
CH₂OH
O
HO
H
H
HO
OH
H
1
O
H
4′
CH₂OH
O
H
H
HO
OH
OH
H
H

Maltose

Since maltose can exist in both α and β forms, the structure of maltose is shown without specifying the configuration of the anomeric carbon (C-1′) that is not an acetal. In α-maltose, the anomeric –OH group is axial, whereas in β-maltose the anomeric –OH group is equatorial. Maltose is a reducing sugar because the right-hand subunit is a hemiacetal and, therefore, remains in equilibrium with the open-chain aldehyde form.

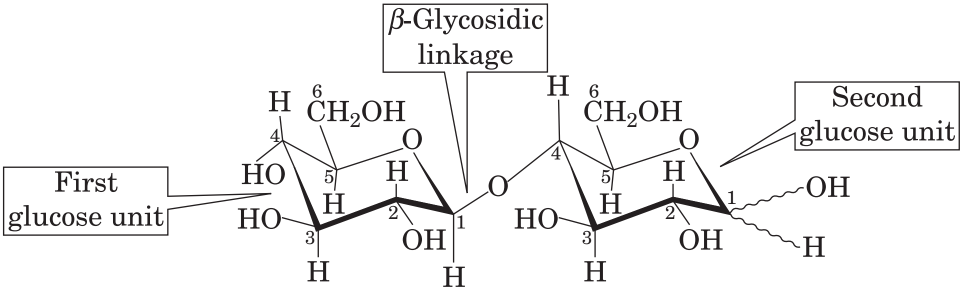
Other common disaccharides are *sucrose*, *lactose* and *cellobiose*.

9.3.1 General Structure of Disaccharides and the Common Glycosidic Bonding Arrangements Found in Naturally Occurring Disaccharides

A disaccharide is a glycoside in which the anomeric –OH group of one monosaccharide unit is bonded by an acetal linkage to any of the hydroxyl groups (anomeric OH or alcoholic OH) of a second monosaccharide unit.

There are three glycosidic bonding arrangement in naturally occurring disaccharides.

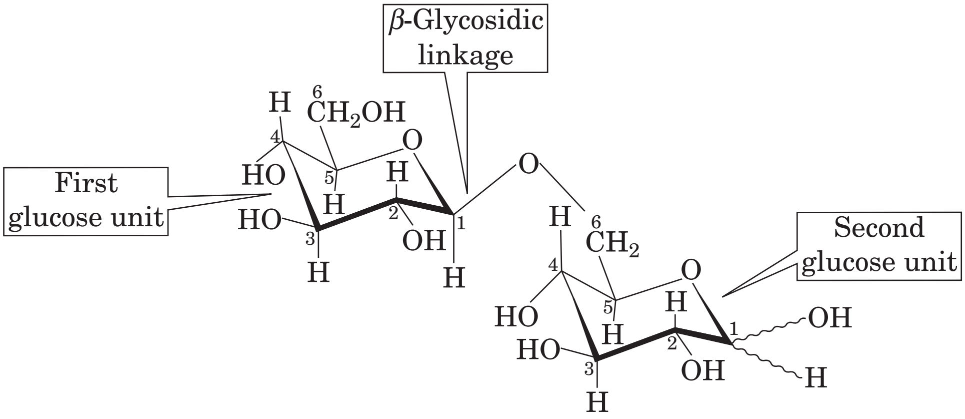
(i) **1,4- linkage:** The anomeric carbon of the first sugar unit is bonded to the oxygen atom on C-4 of the second sugar unit. The 1,4-linkage, for example, present in the disaccharide cellobiose, maltose and lactose. The structure of cellobiose is as follows:



Cellobiose

[The anomeric carbon of the first glucose unit is linked through an equilateral (β) C—O bond to C-4 of the second glucose unit.]

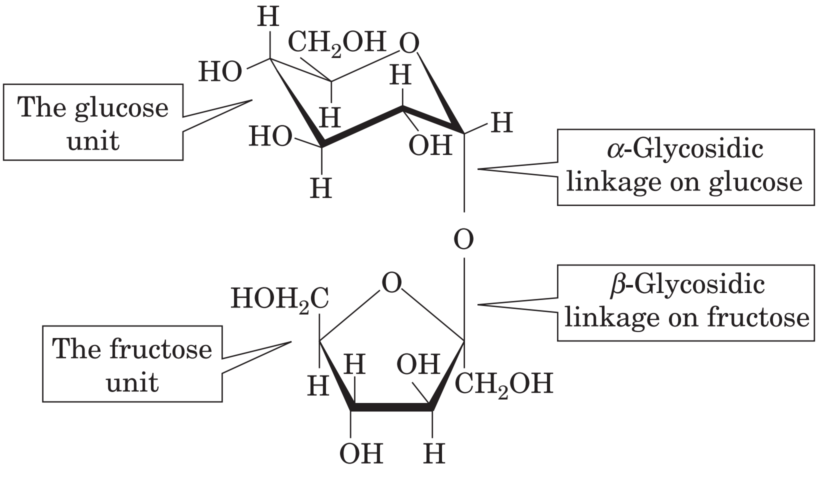
(ii) **1, 6 linkage:** The anomeric carbon of the first sugar unit is bonded to the oxygen atom on C-6 of the second sugar unit. The 1,6 linkage, for example, present in gentiobiose. Its structure is shown below:



Gentiobiose

[The anomeric carbon of the first glucose unit is linked through an equatorial (β) C—O bond to C-6 of the second glucose unit.]

(iii) **1,1 linkage:** The anomeric carbon of the first sugar unit is bonded through an oxygen atom to the anomeric carbon of the second sugar unit. The 1,1 linkage, for example, present in sucrose. Its structure is as follows:



Sucrose

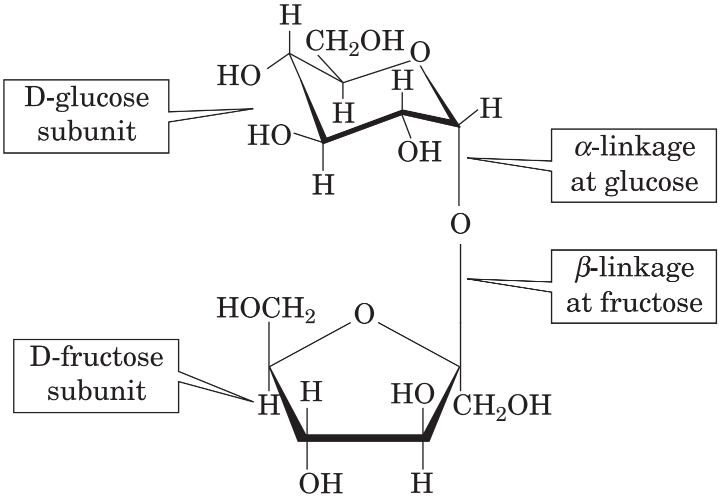
[It is composed of one glucose unit and one fructose unit bonded by an O atom linking their anomeric carbons.]

The 1,4 and 1,6 glycosidic linkages result in formation of reducing disaccharides because in that case one of the sugar unit remains in the hemiacetal form and therefore remains in equilibrium with its open-chain aldehyde form. On the other hand, the 1,1 glycosidic linkage results in formation of non-reducing sugars because in that case both of the monosaccharide units remain as acetal.

9.3.2 Sucrose (case or beet sugar, $C_{12}H_{22}O_{11}$)

Sucrose is the most common disaccharide. It is our common table sugar, obtained from sugar cane and sugar beets. Of organic chemicals, it is the one produced in the largest amount in pure form. About 90 million tons of sucrose are produced in the world each year. Sucrose does not reduce Tollens' or Fehling's reagent. It is a non-reducing sugar and in this respect it differs from other disaccharides like maltose, lactose and cellobiose. Moreover, sucrose does not form an osazone, does not exist in anomeric forms, and does not exhibit mutarotation in solution. All of these observations indicate that sucrose cannot equilibrate to an open-chain form containing a free aldehyde or ketone group.

Sucrose consists of a D-glucose subunit and a D-fructose subunit linked by a glycosidic bond between C-1 of glucose (in the α-position) and C-2 of fructose (in the β-position).

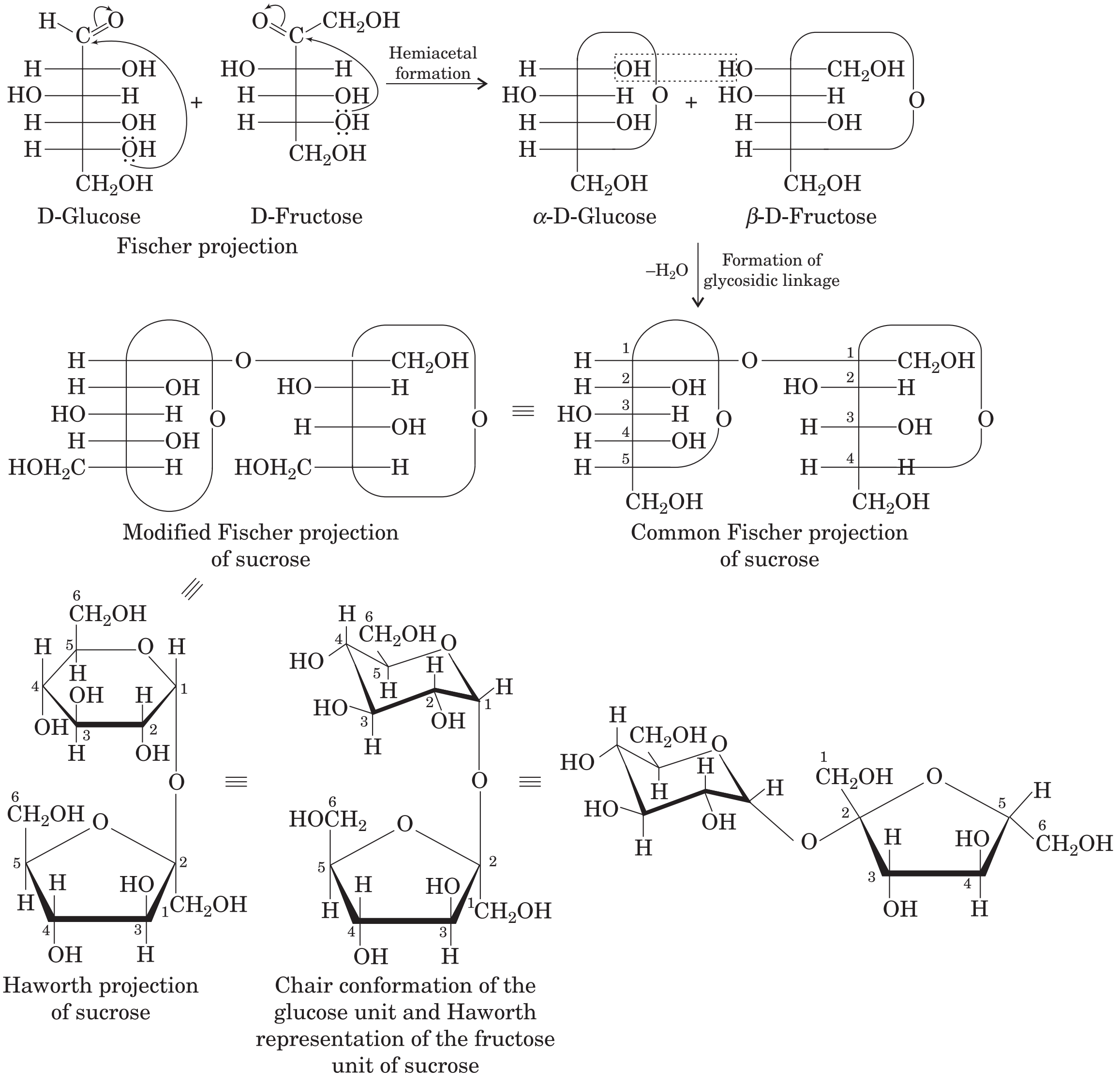


Sucrose

Sucrose is dextrorotatory, $[\alpha]_D = +66.5°$. When it is hydrolyzed by dilute aqueous acid, or by the action of the enzyme *invertase* (from yeast), it yields equimolar amounts of D-(+)-glucose and D-(–)-fructose. Since D-(–)-fructose has a greater specific rotation (–92.4°) than D-(+)-glucose (+52.7°), the resulting 1:1 mixture is levorotatory. The hydrolysis accompanied by a change of rotation from positive to negative is known as the *inversion of cane sugar* and the 1:1 mixture of glucose and fructose is called *invert sugar*.

Honeybees have the enzyme *invertase*, so the honey they produce is mostly inverted sugar, i.e., a mixture of sucrose, glucose and fructose. Inverted sugar is sweeter than sucrose because fructose is sweeter than sucrose.

Fischer, Haworth and Conformational Formulas of Sucrose In sucrose the glucose unit is present as α-anomer and the fructose unit as β-anomer. Then starting from D-glucose and D-fructose one may draw the Fischer, Haworth and conformational formulas as follows:

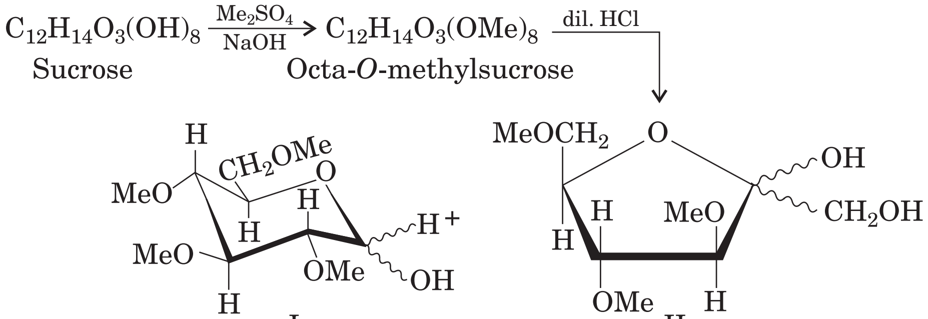

D-Glucose
D-Fructose
Fischer projection
Hemiacetal formation
α-D-Glucose
β-D-Fructose
–H₂O
Formation of glycosidic linkage
Modified Fischer projection of sucrose
Common Fischer projection of sucrose
Haworth projection of sucrose
Chair conformation of the glucose unit and Haworth representation of the fructose unit of sucrose

9.3.2.1 Elucidation of Structure of Sucrose

The structure of sucrose has been established from considerations of the following facts and conclusions therefrom.

1. Elemental analysis and molecular mass determination show that the molecular formula of sucrose is $C_{12}H_{22}O_{11}$.
2. Hydrolysis of sucrose by dilute aqueous acid yields an equimolar mixture of D-(+)-glucose and D-(–)-fructose. This observation suggests that the sucrose molecule is made up of one unit of each of these monosaccharides.

3. Sucrose does not reduce Fehling's and Tollens' reagents. Also, it does not form an oxime or an osazone and does not exhibit mutarotation. This indicates that neither the —CHO group in glucose unit nor the $>C{=}O$ group in fructose unit is free in sucrose. Therefore, a tentative structure of sucrose is one in which the two molecules, glucose and fructose and joined together through glycosidic linkage, i.e., the anomeric carbons of both the glucose and fructose units must be linked through an oxygen bridge in sucrose. Hence, sucrose is a **glucosyl fructoside** or equally, a **fructosyl glucoside**.
4. When sucrose is methylated with Me_2SO_4/NaOH, octa-*O*-methylsucrose is obtained. This, on hydrolysis with dilute HCl, gives 2,3,4,6-tetra-*O*-methyl-D-glucose (I) and 1,3,4,6-*tetra*-*O*-methyl-D-fructose (II).



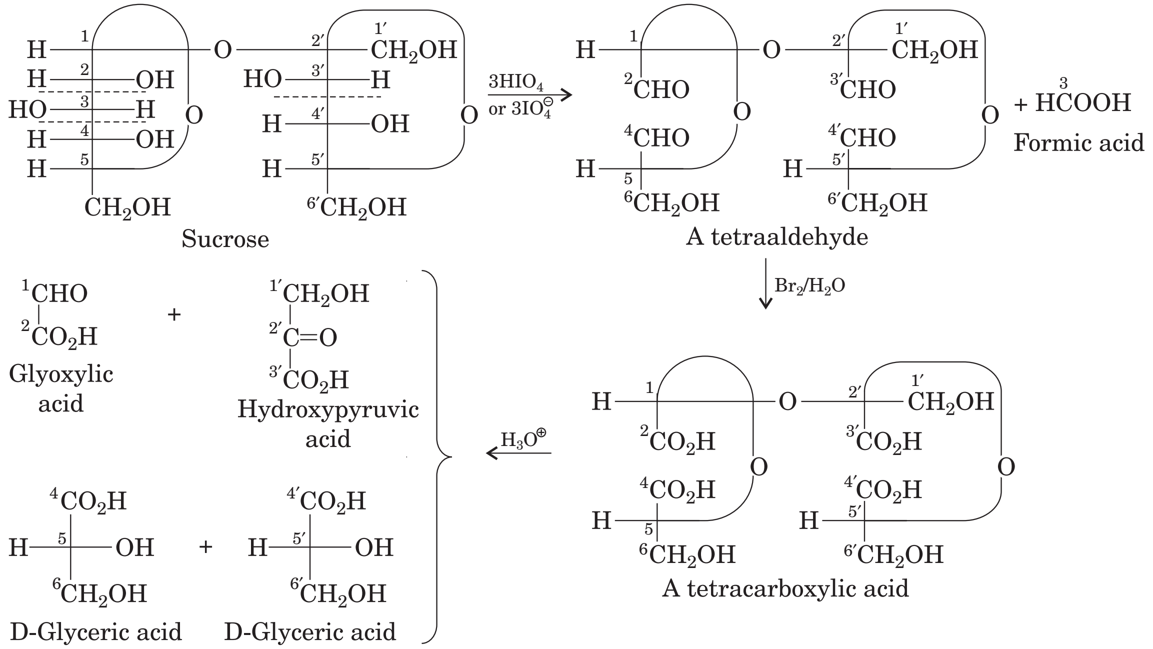
$$\underset{\text{Sucrose}}{C_{12}H_{14}O_3(OH)_8} \xrightarrow[\text{NaOH}]{Me_2SO_4} \underset{\text{Octa-}O\text{-methylsucrose}}{C_{12}H_{14}O_3(OMe)_8} \xrightarrow{\text{dil. HCl}}$$

I
2,3,4,6-Tetra-*O*-methyl-
D-glucopyranose

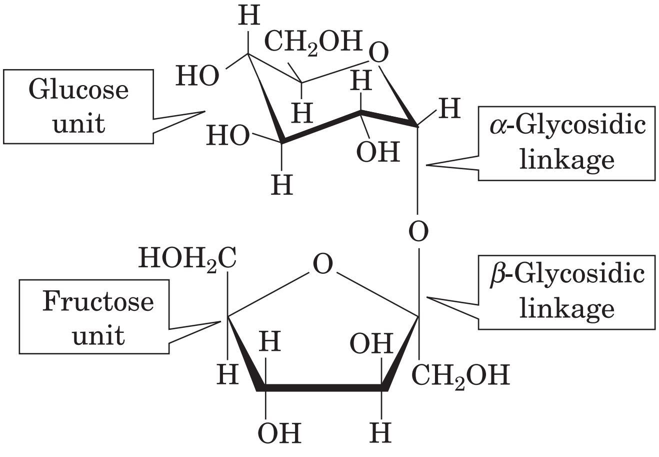
II
1,3,4,6-Tetra-*O*-methyl
D-fructofuranose

It has been determined by oxidation method that methyl groups are absent on C-5 of these two products. This clearly indicates that the –OH groups located on these carbons are involved in formation of the oxide ring. It thus becomes clear that the glucose and fructose units in sucrose are present as six-membered (pyranose) and five-membered (furanose) ring, respectively.

The size of the two rings in sucrose may also be determined by periodic acid oxidation. Sucrose consumes three moles of periodic acid, whereby one mole of formic acid and one mole of a tetraaldehyde are formed. When this tetra aldehyde is oxidized with bromine-water and the resulting tetracarboxylic acid is hydrolyzed by dilute acid 3-hydroxy-2-oxopropanoic acid (hydroxypyruvic acid, $HOCH_2COCO_2H$), oxoethanoic acid (glyoxylic acid, OHC—CO_2H) and D-glyceric acid ($HOCH_2CHOHCO_2H$) are obtained. From these products it has further been established that the glucose unit in sucrose is present as a six-membered (pyranose) ring and the fructose unit is present as a five-membered (furanose) ring.



5. The stereochemical nature of the glycosidic links, i.e., the anomeric configurations may be known from the result of enzymetic hydrolysis of sucrose. It is known that enzymes are highly specific catalysts for the hydrolysis of different types of glycosidic linkages. The enzyme *maltose*, for example, catalyzes specifically the hydrolysis of α-glucosidic bond. Since this enzyme hydrolyses sucrose, the glucose residue in sucrose is present as an α-glucoside. Similarly, the enzyme *invertase* which specifically catalyses the hydrolysis of β-fructosides, also hydrolyses sucrose. Therefore, the fructose residue in sucrose is present as β-anomer.
From the above facts and conclusions therefrom the structure of sucrose is as follows:



(+)-Sucrose

The results of X-ray studies and the synthesis of (+)-sucrose (1953) lead to the conclusion that (+)-sucrose is a *beta* D-fructoside and *alpha* D-glucoside. Sucrose may, therefore, be called either α-D-glucopyranosyl-β-D-fructofuranoside or β-D fructofuranosyl-α-D-glucopyranoside.

SOLVED PROBLEMS

1. **How do you account for the experimentally observed $[\alpha]_D$ = –19.9° for invest sugar?**

Solution D-(+)-Glucose has a specific rotation of +52.7° and D-(–)-fructose has a specific rotation of –92.4°. The specific rotation of inverted sugar is one-half the sum of those of the individual monosaccharides.

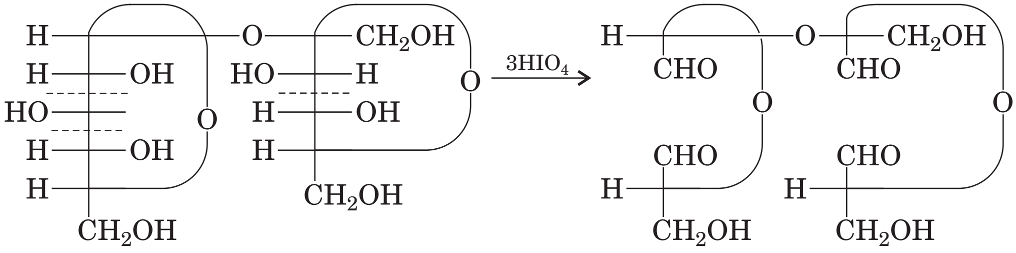
$$\frac{1}{2}[+52.7° + (-92.4°)] = -19.9°$$

2. **Explain why sucrose is not a reducing sugar and does not exhibit mutarotation.**

Solution Sucrose is made up of a D-glucose unit and a D-fructose unit linked by a glycosidic bond between C-1 of glucose and C-2 of fructose. Both the carbonyl functions in sucrose are blocked as acetal. Because sucrose does not have a hemiacetal group, it is not in equilibrium with the readily oxidizable open-chain aldehyde or ketone form in aqueous solution. Because of this, it is not a reducing sugar and does not exhibit mutarotation.

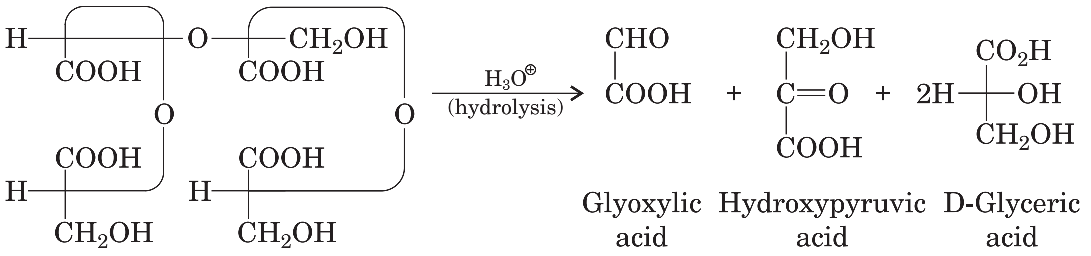
3. **Explain why it requires three moles of HIO_4 for the oxidative cleavage of sucrose.**

Solution In glucose unit of sucrose, there is a —CH(OH)—CH(OH)—CH(OH)— moiety and in fructose unit, there is a —CH(OH) —CH(OH) — moiety. Since HIO_4 cleaves the bond between two OH containing carbon atoms, it requires two moles of HIO_4 for the glucose unit and one mole HIO_4 for the fructose unit. Hence, it requires 3 moles of HIO_4 for the oxidative cleavage of sucrose.

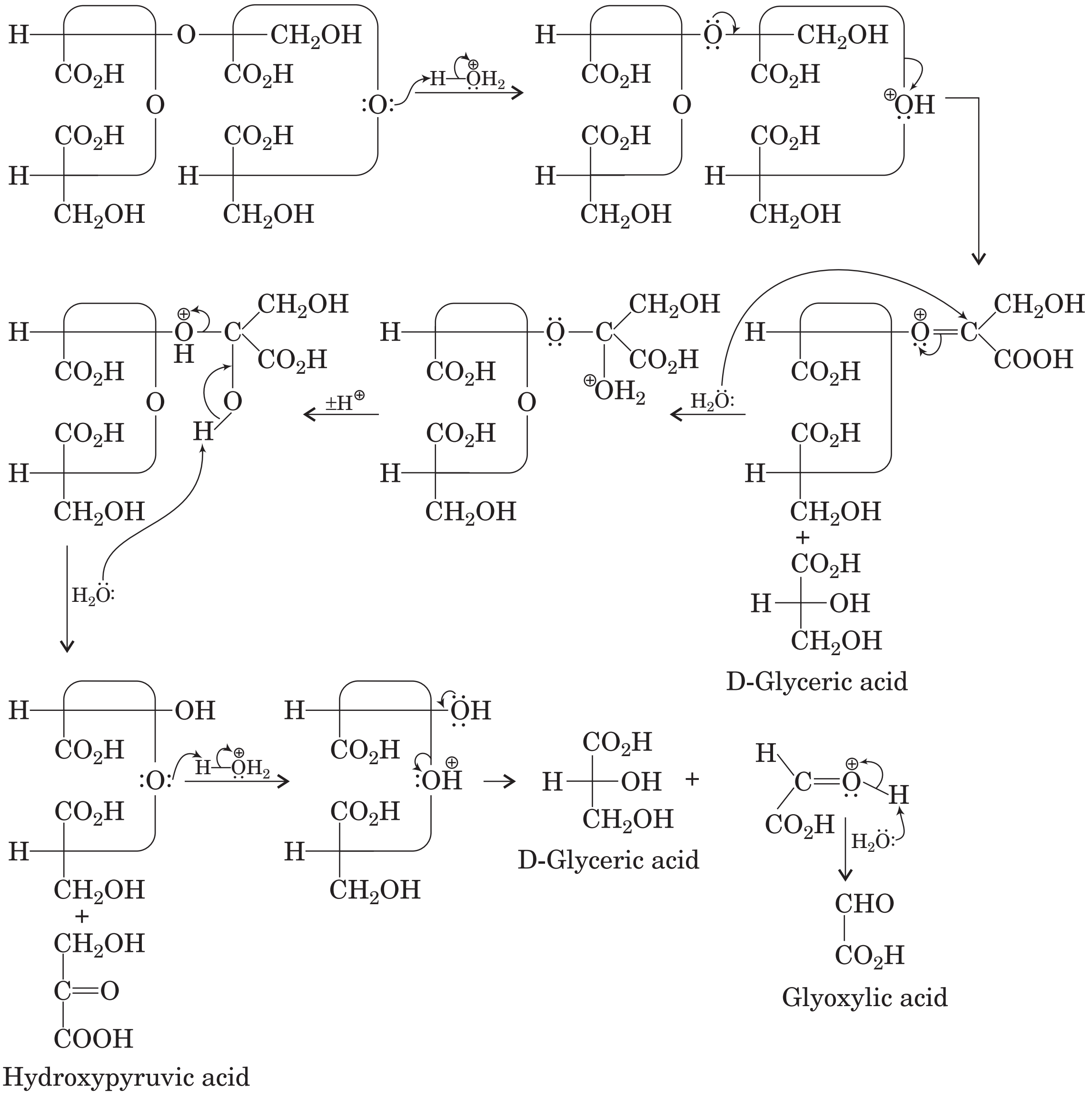


A tetraaldehyde
+
HCOOH
Formic acid

4. Suggest a mechanism for the following reaction:

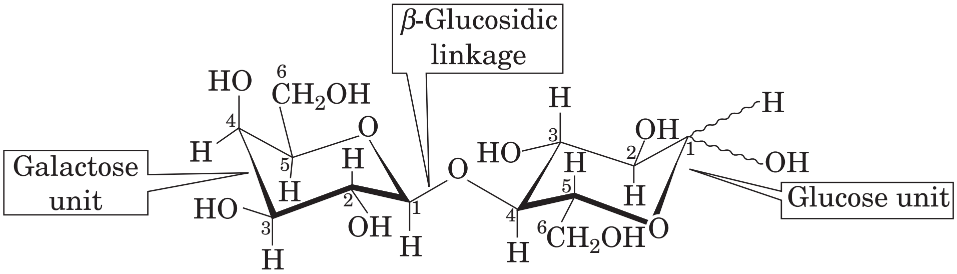


Solution This acetal undergoes hydrolysis in the presence of dilute acid as follows:



5. Write the IUPAC name and structure of a disaccharide which is a reducing sugar. Explain why it is reducing in nature.

Solution Lactose is a reducing sugar. Its structure is as follows:



Chair conformation of lactose

Its IUPAC name is 4-*O*-(*β*-D-galactopyranosyl)-D-glucopyranose.

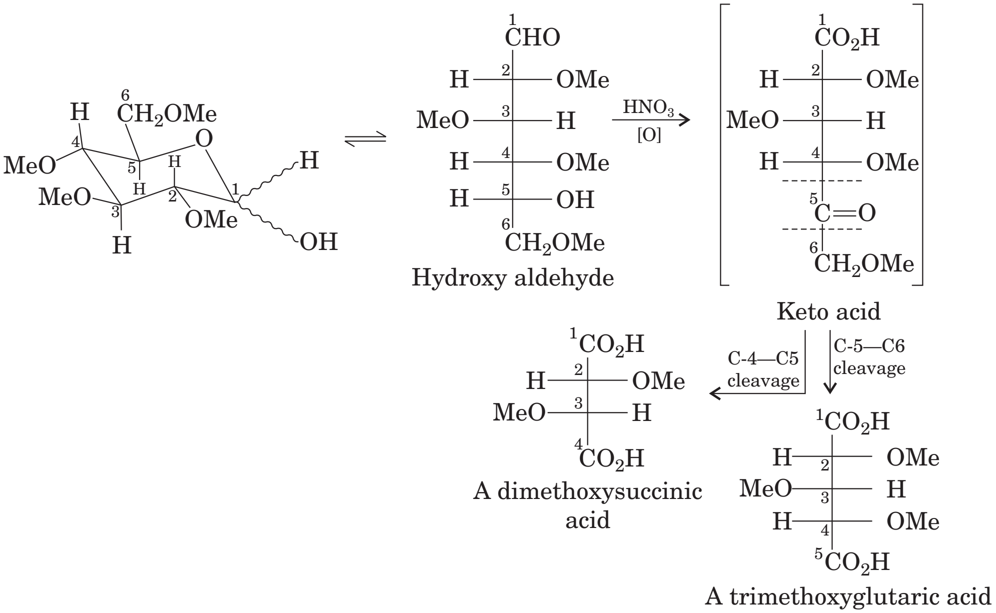
Lactose has a free hemiacetal ring (the glucose unit). This hemiacetal is in equilibrium with its open-chain form. Because of this, lactose is a reducing sugar.

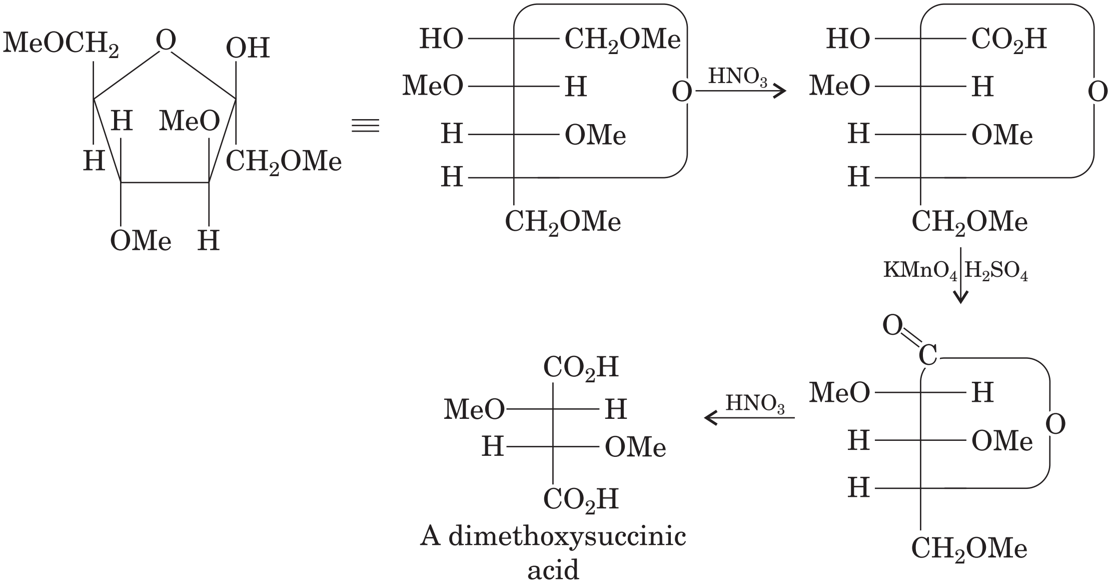
6. (a) Write equations for the sequence of methylation and hydrolysis as appled to (+)-sucrose. (b) What compounds are expected to be obtained when the final products of (a) are subjected to oxidative cleavage.

Solution

(a) See **article no. 9.3.2.1.**

(b)





A dimethoxysuccinic acid

STUDY PROBLEMS

1. Mention a chemical test that will distinguish between sucrose and maltose.
2. Account for the fact that sucrose is a non-reducing sugar but reduces Fehling's solution after heating with dilute HCl.
3. What is invert sugar and why is it so named?
4. Draw common types of glycosidic linkages and recognize these linkages in disaccharides and polysaccharides.
5. Explain why maltose are lactose and reducing but sucrose is non-reducing.
6. Explain why dextrorotatory sucrose solution shows a gradual drop in optical rotation with time in aqueous HCl until it shows no optical rotation and after that it begins to show laevorotation.

   [**Hint:** Sucrose ($[\alpha]_D = +66.5°$) on hydrolysis yields equimolar amounts of D-glucose ($[\alpha]_D = +52.7°$) and D-fructose ($[\alpha]_D = –92.4°$). The solution of sucrose in aqueous HCl shows a gradual drop of optical rotation because the amount of fructose with higher negative rotation gradually increases and the amount of sucrose decreases. When the amounts of sucrose, glucose and fructose is such that the mean rotation of the components is zero, the solution shows no optical rotation. When the amount of fructose increases more, the mean rotation becomes negative, and then the solution begins to show laevorotation.]

7. Write the Haworth structure of D-sucrose.

8. Prove that the glucose portion of sucrose is a pyranoside and the fructose portion is a furanoside.

9. When (+)-sucrose is hydrolyzed enzymatically, the D-glucose initially obtained mutarotates downward to +52.7°. What does this fact suggest about the structure of (–)-sucrose?

[**Hint:** Sucrose is an α-glucoside.]

10. What would be the molecular formula of (+)-sucrose if C-1 of the glucose unit remains attached to, say, C-4 of the fructose unit, and C-2 of the fructose unit remains attached to C-4 of the glucose unit? Would this sugar be a reducing or a non-reducing one?

[**Hint:** $C_{12}H_{20}O_{10}$; non-reducing]

11. (a) Comment on the general structure of disaccharides.

(b) What sequence is used for drawing the monosaccharide units present in disaccharides?

[**Hint:** (a) A disaccharide is a glycoside in which the anomeric OH of one monosaccharide is bonded by an acetal linkage to an –OH group of a second molecule of monosaccharide, called the *aglycone*. The aglycone contains a typical ether linkage.

(b) The aglycone is the end monosaccharide unit on the right.]

12. Sucrose crystallizes much more readily than most sugars, a fact that has been associated with the fact that it does not undergo mutarotation. How might absence of mutarotation contribute to the ease of crystallization?

13. Explain why sucrose can be called fructosyl glucoside or a glucosyl fructoside.

14. Sucrose can be cleaved using three equivalents of periodic acid or sodium periodate. Outline the course of that oxidative cleavage.

15. (a) What monosaccharides will be formed by the acid-catalyzed hydrolysis of sucrose?

(b) Provide a mechanism for this reaction.

16. Sucrose does not exhibit mutarotation when dissolved in water, but when sucrose is warmed with dilute acid its rotation changes from positive value to a negative value. Explain.

17. What happens when sucrose is subjected to periodic acid oxidation followed by treatment with Br_2/H_2O and hydrolysis with aqueous acid?

18. Give the products obtained from the acid-catalyzed hydrolysis of completely methylated sucrose.

19. Give the IUPAC names of sucrose.

9.4 POLYSACCHARIDES

Polysaccharides are naturally occurring polymers, which can be considered as derived from aldoses or ketoses by polymerization involving loss of water. These polymers contain as many as several thousands of monosaccharide units per molecule. As in disaccharides these units are held together by glycosidic linkages, which can be cleaved by hydrolysis. A polysaccharide derived from hexoses, for example, has the general formula $(C_6H_{10}O_5)_n$. As with other polymers, it is important to know (i) which specific monomers are involved in polymer information, (ii) the method of linkage between the monomers, and (iii) the gross structure of the polymer. If the polymer contains more than one type of monosaccharide, then the sequence of sugars is also important.

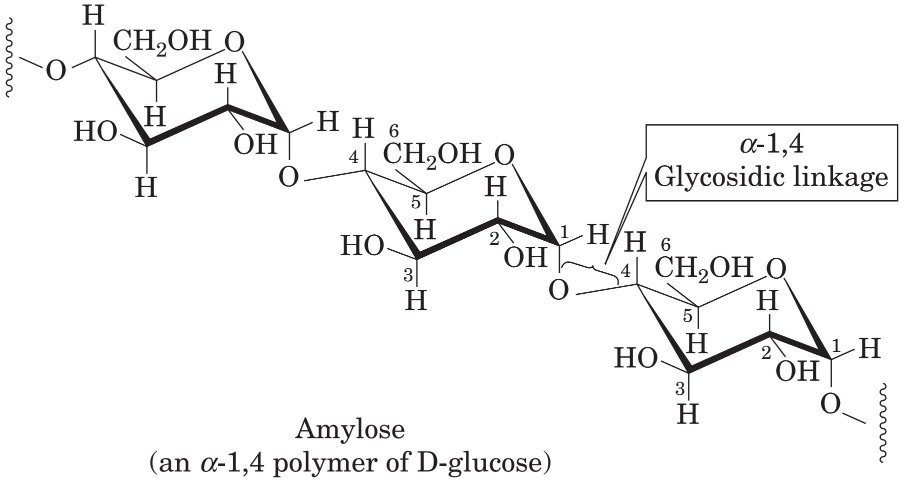
The two most important naturally occurring polysaccharides are *starch* and *cellulose*. Both of these are produced in plants from CO_2 and water by the process of photosynthesis and both are made up of D-(+)-glucose units. Cellulose is the chief structural material of plants, giving plants rigidity and form. It plays a vital role in our society. As wood, cellulose provide shelter; as wood pulp, it is the basis of paper without which it is hard to imagine our civilization. Cellulose is also the major constituent of cotton, the most important natural fibre. Starch is the mainstay of many diets, since it is the major compound present in rice, potatoes, wheat, and corn. It is more soluble in water compared to cellulose, more easily hydrolyzed, and hence more readily digested.

9.4.1 Starch

Starch is the major source of energy in plant cells. It occurs as granules whose size and shape are characteristic of the plant from which it is isolated. In general, starch contains about 20% of a water-soluble fraction called **amylose** and 80% of a water-insoluble fraction called **amylopectin**. Both of these can be hydrolyzed in acid to give only D-glucose. This behaviour suggests that, since both polymers contain the same monomer, the important difference between them must exist in the style of bonding within these polymers.

9.4.1.1 Structure of amylose

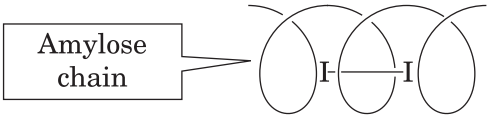
(+)-Maltose is the only disaccharide and D-(+)-glucose is the only monosaccharide that are obtained by hydrolysis of amylose. To account for this observation, it has been proposed that amylose is made up of chains of many D-(+)-glucose units, each unit joined by an α-glycosidic linkage to C-4 of the next unit. A partial structure of amylose is shown as follows:



Amylose
(an α-1,4 polymer of D-glucose)

Physical measurement suggest that the molecular mass of amylose is about 40,000, i.e., it is a polymer containing upwards of 200 monosaccharide units. This is supported by chemical analysis.

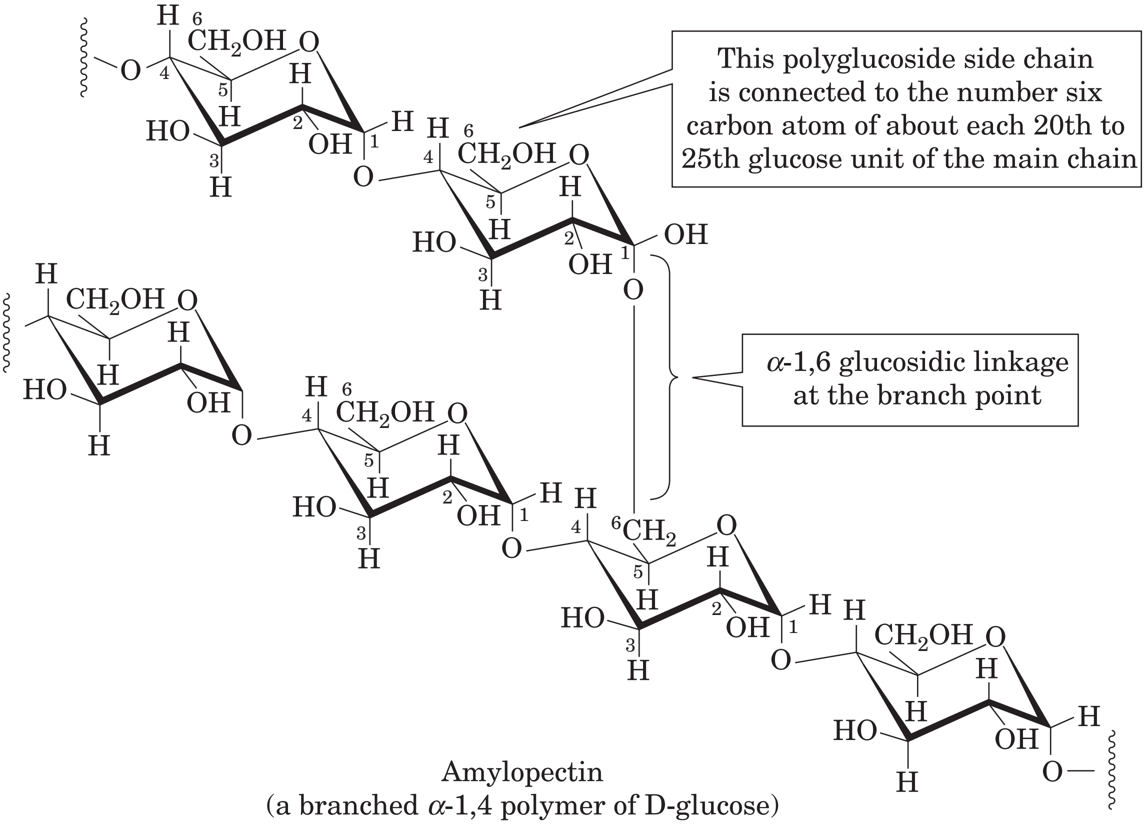
Starch-iodine Test The famous starch-iodine test, the development of a blue colour when starch is mixed with iodine, is better considered an 'amylose-iodine test' since it is the amylose in starch that is responsible for most of the colour. It is believed that the helical structure of amylose serves as the basis for this interesting and useful test for starch (as well as for iodine). The inside of the helix is just the right size and polarity to accept an iodine (I_2) molecule. When iodine is trapped by amylose within this helix, a deep blue starch-iodine charge-transfer complex is formed. At high temperatures, the helix partially unwinds and then fewer iodine molecules are trapped to give reddish brown colour. On cooling, the helix reforms, enclosing more iodine molecules, and the original blue colour is redeveloped.



Amylose–iodine complex
(deep-blue)

9.4.1.2 Structure of Amylopectin

Amylopectin is hydrolyzed to the disaccharide (+)-maltose. Therefore, like amylose, it is also made up of chains of D-glucose units; each unit is joined by an α-glycosidic linkage to C-4 of the next one. That is, it is also primarily an α-1,4 polymer of D-glucose. Its structure is, however, more complex than that of amylose. The difference between amylose and amylopectin is that the latter has a highly branched structure consisting of several branched short chains of about 20–25 D-glucose units each. The chain, which starts at each branch point, is connected to the main chain by an α-1,6 glycosidic linkage. A partial structure of amylopectin, including one branch point is shown below:


This polyglucoside side chain is connected to the number six carbon atom of about each 20th to 25th glucose unit of the main chain
α-1,6 glucosidic linkage at the branch point

Amylopectin
(a branched α-1,4 polymer of D-glucose)

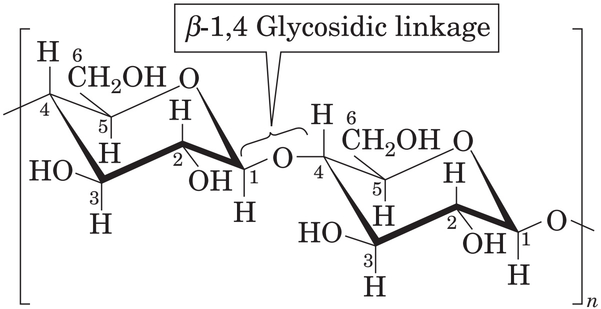
Physical measurements indicate that amylopectin has a molecular weight of one to six million; therefore, amylopecton consists of hundreds of interconnecting chains of 20–25 glucose units each.

9.4.2 Cellulose

Cellulose is the main constituent of plant cell walls. Cotton and flux are over 90% cellulose and wood is 40–50% cellulose. Hydrolysis of cellulose produces D-glucose. Humans do not have enzymes that can hydrolyze cellulose and thereby utilize its component glucose. Cellulose undergo hydrolysis by a group of enzymes known as *cellulases*. The cellulases, which are generated by bacteria and fungi, are capable of breaking the β-glucoside linkage. Cud-chewing animals like cows, as well as insect pests, termites, can utilize cellulose as a source of glucose and this is because they possess parasitic bacteria which provide this particular group of enzymes.

9.4.2.1 Structure of Cellulose

The structure of cellulose is a linear sequence of glucose units linked by 1,4-glucoside bonds. In cellulose, all the glucosidic configurations are β. The poly-β-glucoside structure is an energetically favourable configuration because all substituents are placed in equatorial position.



Cellulose
(a β-1,4 polymer of D-glucose)

SOLVED PROBLEMS

1. **Write down the names of two ubiquitous plant polysaccharides consisting of only D-glucose units.**

Solution Starch and cellulose are the two ubiquitous plant polysaccharides consisting of only D-glucose units.

2. **Amylose (the water-soluble portion of starch) is hydrolyzed partially to maltose and α-D-glucose. On methylation followed by hydrolysis, 2,3,6-tri-*O*-methyl-D-glucopyranose is mainly obtained. Comment on the structure of amylose.**

Solution Amylose is composed of maltose units strung together in a chain where the anomeric –OH of one glucose unit is bonded to the C-4 –OH of another glucose unit. Formation of α-D-glucose indicates that the glycosidic linkage is α.

3. **What do you mean by glycogen? How does it differ from starch?**

Solution Glycogen is the reserve polysaccharide of animals, whereas starch is the reserve polysaccharide for plants.

4. **What is cellulose? What is the structural difference between cellulose and starch?**

Solution Cellulose (a polymer of glucose units linked by β-1,4-glycosidic linkage) is the most abundant naturally occurring organic compound on earth. It is the chief component of wood and plant fibres.

Cellulose differs from starch is having β-1,4-glucosidic linkages and not α. Also, it contains more glucose units, giving it a higher molecular mass.

5. **Do amylose and amylopectin give the same colour with iodine? Give your reasoning.**

Solution Although amylose gives a deep blue colour with iodine, amylopectin gives a less intense red-brown colour because the helical structure is disrupted by the branching of the chain.

6. **When amylose is methylated with Me_2SO_4/NaOH and then hydrolyzed, about 0.5% of the product is 2,3,4,6-tetra-*O*-methyl-D-glucose is obtained. Explain the origin of this compound.**

Solution 2,3,4,6-Tetra-*O*-methyl-D-glucose is obtained by the reaction of the glucose unit at the left end of the polymer which has a free C-4 OH.

7. What is dextrin (corn syrup)?

Solution Mild hydrolysis of starch with dilute acid produces dextrin (corn syrup) which is, in fact, a mixture of maltose, D-glucose and branched oligosaccharides. It is often a component of infant diets because it is easily digested.

STUDY PROBLEMS

1. What is the major source of energy in plant cells?

2. What are the two major fractions of starch?

3. Why do the cellulose molecules remain relatively intact when various pulping processes are carried out?

4. Which enzyme, found in plants, hydrolyzes starch to maltose.
[**Hint:** β-amylase.]

5. Indicate how the three polymethyl D-glucose molecules obtained on methylation followed by hydrolysis of amylopectin support the proposed structure. How would the products obtained on similar treatment of amylose differ?

6. Write down two major nonnutritional applications of starch.
[**Hint:** The two major nonnutritional applications of starch are as sizing agents to improve the strength of fabrics and the writing quantities of paper surfaces.]

7. What is the reason of general resistance of cellulose to chemical reactions?
[**Hint:** Its fibrous structure.]

8. The markedly different water solubilities of amylose and amylopectin is due to the gross structural difference between them. Explain.

9. Starch is a non-reducing polysaccharide derived from D-(+)-glucopyranose. What conclusion can be drawn from this fact regarding the structure of starch? Give a partial structure of starch in Haworth projection.

10. What is cellulose? What is its main constituent. Give its partial structure in Fischer as well as Haworth projections.

11. Write down a simple test for starch. Indicate the change that occurs when the test is performed at elevated temperatures.

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Amino Acids, Peptides, Proteins and Nucleic Acids

10

Chapter Outline

Introduction

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  - 10.1.1 Nomenclature, Classification and Structure of Amino Acids
  - 10.1.2 Configuration of Natural Amino Acids
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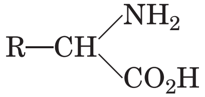
INTRODUCTION

Living organisms produce three types of organic polymers, called biopolymers, which are, in fact, essential for life processes. These three important groups of biological polymers are polysaccharides, proteins and nucleic acids. We studied polysaccharides in Chapter 9. Polysaccharides function mainly as energy reserves, as biochemical labels on cell surfaces, and, in plants, as structural materials. In this chapter, we will study proteins and nucleic acids. Among the three major classes of biomolecules, proteins have the widest array of functions. As molecules, they form critical structures. Keratin and collagen, for example, are part of a large group of structural proteins that form long insoluble fibres, which give strength and support to tissues. Skin, hair, horns and nails are all made up of keratin. Collagen is found in connective tissue, tendons, cartilage and bone. Our body is thereby provided with the means for movement. As enzymes they serve as catalyst to affect chemical reactions and thereby regulate all aspects of cellular function. As hormones they control many body functions, including, metabolism, growth and reproduction. Insulene, the hormone that regulates blood glucose levels, hemoglobin, which transport oxygen from lungs to all the tissues, and fibrinogen and thrombin, which form blood clots, are all proteins.

Nucleic acids serve two major purposes: storage and transmission of information. There are two types of nucleic acids: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA encodes an organism's entire hereditary information and controls the growth and division of cells. In almost all organisms, the genetic information stored in DNA is transcribed into RNA. This information is then translated for the synthesis of all the proteins required for cellular structure and functions. For these reasons, we have to know the structures and properties of these nucleic acids and of their components, nucleotides and nucleosides.

10.1 AMINO ACIDS

Chemically peptides and proteins are polyamides of α-amino acids (carboxylic acids containing an amino group at C-2 or α-position).

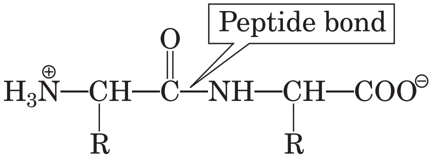


An α-amino acid

(R is a side chain at the α carbon that determines the identity of the amino acid)

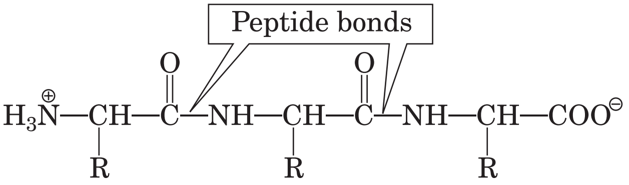
The α-amino acids, which are normally obtained from naturally occurring proteins by the process of hydrolysis, are twenty in number and therefore, these α-amino acids are the building blocks of proteins. Ten of these α-amino acids are called *essential amino acids*.

An amide bond (—CO—NH—) between the carboxylic acid function of an amino acid and the amino nitrogen of another is called *peptide bond* or *peptide linkage*. α-Amino acids are linked together by peptide bonds in proteins. A dipeptide is a molecule consisting of two amino acids joined by a peptide bond. A tripeptide has three amino acids joined by two peptide bonds, a tetrapeptide has four amino acids, and a polypeptide contains many. Proteins are naturally occurring polypeptides made up of 40–4000 amino acid units, and so, the molecular mass of most proteins are much larger. They have important biological function.



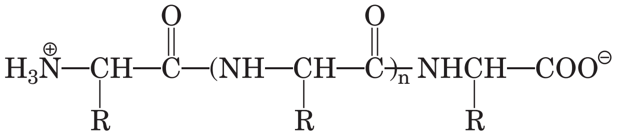
$$H_3\overset{\oplus}{N}-\underset{R}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-NH-\underset{R}{\underset{|}{CH}}-COO^{\ominus}$$

A dipeptide



$$H_3\overset{\oplus}{N}-\underset{R}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-NH-\underset{R}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-NH-\underset{R}{\underset{|}{CH}}-COO^{\ominus}$$

A tripeptide



$$H_3\overset{\oplus}{N}-\underset{R}{CH}-\overset{O}{\overset{\|}{C}}-(NH-\underset{R}{CH}-\overset{O}{\overset{\|}{C}})_n-NH\underset{R}{CH}-COO^{\ominus}$$

A polypeptide or
protein

The name protein is taken from the Greek *proteios* which means *first*. The choice of the name rests upon the fact that of all chemical compounds, proteins must almost certainly ranked first, for they are the substance of life.

10.1.1 Nomenclature, Classification and Structure of Amino Acids

10.1.1.1 Nomenclature of Amino Acids

Amino acids can be named according to the IUPAC convention, but they are generally known by their common names. For example, the amino acid NH_2CH_2COOH is known as glycine instead of 2-aminoethanoic acid.

The common names of the amino acids are assigned on the basis of their source and properties. Glycine, for example, is named so, because it tastes sweet (Greek word '*glykos*' means sweet). Similarly, tyrosine was first isolated from cheese (Greek word '*tyros*' means cheese), and so on. The names of the amino acids are generally written in their three-letter abbreviated form such as *gly* for glycine, *ala* for alanine, etc. Sometimes one-letter abbreviations are also used.

10.1.1.2 Classification of Amino Acids

(a) Classification based on the number $—NH_2$ and —COOH groups

(i) **Neutral amino acids:** Amino acids containing same number of $—NH_2$ and —COOH groups are known as neutral amino acids. These are further classified as follows: 1. amino acids containing aliphatic side chain, 2. hydroxy-containing amino acids, 3. sulphur containing amino acids, 4. benzene containing amino acids, 5. heterocyclic amino acids and 6. amide containing amino acids or amides of acidic amino acids.

Examples: Glycine, valine, phenylalanine, etc.

(ii) **Acidic amino acids:** Amino acids with an additional —COOH group in the side chain are called acidic amino acids. When the amino acid contains a potential carboxyl group in the form of a carboxamide ($—CONH_2$), it is also considered as an acidic amino acid.

Examples: Aspartic acid, asparagine, etc.

(iii) **Basic amino acids:** Amino acids with an additional basic group like an amino group, a guanidino group or an imidazole ring in the side chain are called basic amino acids.

Examples: Lysine, histidine, etc.

(b) Classification based on ability of synthesis of human metabolic processes

(i) **Essential amino acids:** Human body cannot synthesize 10 amino acids out of 20 obtained from protein. So, these amino acids must be taken through diet. Normal growth and development of the body are retarded when there is a deficiency of these amino acids. These 10 amino acids are called *essential amino acids*. These are valine, leucine, isoleucine, phenylalanine, methionine, trytophan, threonine, arginine, histidine and lysine.

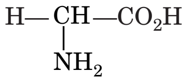
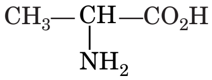
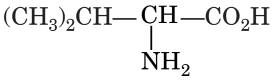
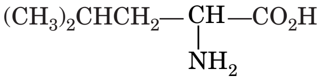
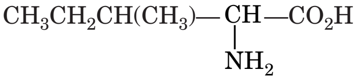
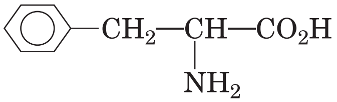
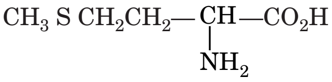
(ii) **Non-essential amino acids:** The amino acids which are synthesized by human metabolic possesses are called non-essential amino acids. All amino acids except the 10 essential amino acids are non-essential amino acids.
Examples: Glycine, alanine, serine, cysteine, cystine, tryptophan, tyrosine, etc.

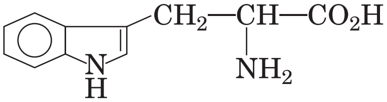
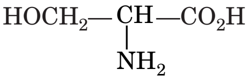
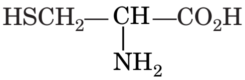
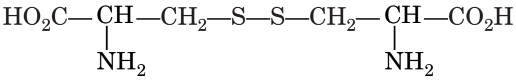
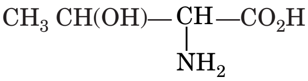
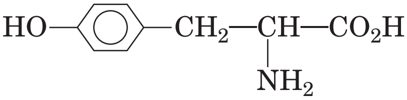
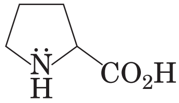
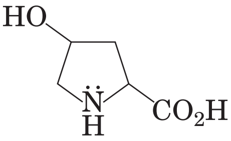
(c) Structure of amino acids

The following table gives the structures and names of 23 amino acids of which only 20 are actually used by cells when they synthesize proteins. Certain of these (marked *e*) are *essential* amino acids.

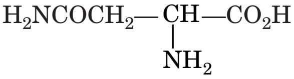
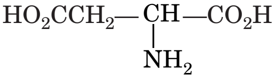
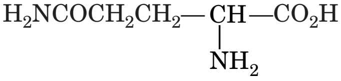
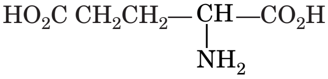
Natural Amino Acids

1. Neutral Amino Acids

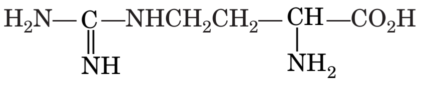
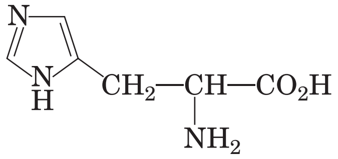
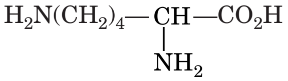
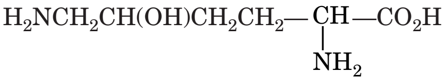
Name	Abbreviations	Structure
1. Glycine	Gly or G	 $\mathrm{H-\underset{\underset{NH_2}{\vert}}{CH}-CO_2H}$
2. Alanine	Ala or A	 $\mathrm{CH_3-\underset{\underset{NH_2}{\vert}}{CH}-CO_2H}$
3. Valine^e	Val or V	 $\mathrm{(CH_3)_2CH-\underset{\underset{NH_2}{\vert}}{CH}-CO_2H}$
4. Leucine^e	Leu or L	 $\mathrm{(CH_3)_2CHCH_2-\underset{\underset{NH_2}{\vert}}{CH}-CO_2H}$
5. Isoleucine^e	Ile or I	 $\mathrm{CH_3CH_2CH(CH_3)-\underset{\underset{NH_2}{\vert}}{CH}-CO_2H}$
6. Phenylalanine^e	Phe or F	
7. Methionine^e	Met or M	 $\mathrm{CH_3\ S\ CH_2CH_2-\underset{\underset{NH_2}{\vert}}{CH}-CO_2H}$

8. Tryptophan^e	Trp or W	
9. Serine	Ser or S	 $HOCH_2-\underset{NH_2}{\underset{\vert}{CH}}-CO_2H$
10. Cysteine	Cys or C	 $HSCH_2-\underset{NH_2}{\underset{\vert}{CH}}-CO_2H$
11. Cystine	Cys-Cys	 $HO_2C-\underset{NH_2}{\underset{\vert}{CH}}-CH_2-S-S-CH_2-\underset{NH_2}{\underset{\vert}{CH}}-CO_2H$
12. Threonine^e	Thr or T	 $CH_3\ CH(OH)-\underset{NH_2}{\underset{\vert}{CH}}-CO_2H$
13. Tyrosine	Tyr or Y	
14. Proline	Pro or P	
15. Hydroxyproline	Hyp	

2. Acidic Amino Acids

Name	Abbreviations	Structure
16. Asparagine	Asn or N	 $H_2NCOCH_2-\underset{NH_2}{\underset{\vert}{CH}}-CO_2H$
17. Aspartic acid	Asp or D	 $HO_2CCH_2-\underset{NH_2}{\underset{\vert}{CH}}-CO_2H$
18. Glutamine	Gln or Q	 $H_2NCOCH_2CH_2-\underset{NH_2}{\underset{\vert}{CH}}-CO_2H$
19. Glutamic acid	Glu or E	 $HO_2C\ CH_2CH_2-\underset{NH_2}{\underset{\vert}{CH}}-CO_2H$

3. Basic Amino Acids

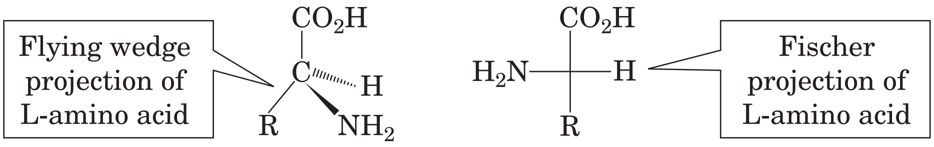
Name	Abbreviations	Structure
20. Arginine^e	Arg or R	 $\mathrm{H_2N{-}\underset{\overset{\|}{NH}}{C}{-}NHCH_2CH_2{-}\underset{\overset{\mid}{NH_2}}{CH}{-}CO_2H}$
21. Histidine^e	His or H	
22. Lysine^e	Lys or K	 $\mathrm{H_2N(CH_2)_4{-}\underset{\overset{\mid}{NH_2}}{CH}{-}CO_2H}$
23. Hydroxylysine	Hyl	 $\mathrm{H_2NCH_2CH(OH)CH_2CH_2{-}\underset{\overset{\mid}{NH_2}}{CH}{-}CO_2H}$

***e* indicates essential amino acids**

It is to be noted that proline and hydroxyproline are secondary amines in which the amino nitrogens are incorporated into five-membered rings.

10.1.2 Configuration of Natural Amino Acids

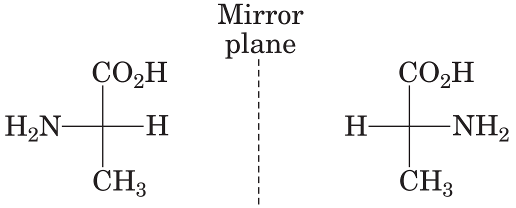
All naturally occurring amino acids except glycine ($H_2NCH_2CO_2H$) have an asymmetric α-carbon atom and are chiral molecules. These chiral amino acids are found in nature in one enantiomeric form, which has the following configuration:


Flying wedge projection of L-amino acid
CO₂H
C
H
R
NH₂
CO₂H
H₂N
H
R
Fischer projection of L-amino acid

Configuration of naturally occurring amino acids

This configuration in *S* in all cases except for cysteine in which —R (i.e., the —CH_2SH group) gets priority over —COOH.

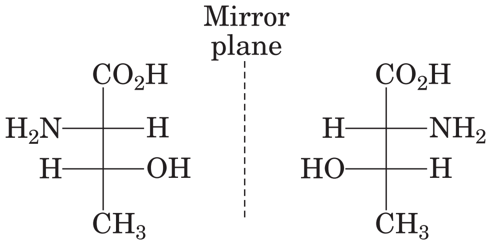
The stereochemistry of amino acids is often specified with D,L-system. An amino acid drawn in Fisher projection with the carboxyl group at the top and the R group at the bottom of the vertical axis is a D-amino acid if the amino group is on the right and an L-amino acid if the amino group is on the left. Therefore, all naturally occurring amino acids have the L-configuration (unlike monosaccharides where the D-isomer is the one found in nature). Thus, (*S*)-alanine can also be called L-alanine; its enantiomer is D-alanine.



L-Alanine
(*S*)-Alanine

D-Alanine
(*R*)-Alanine

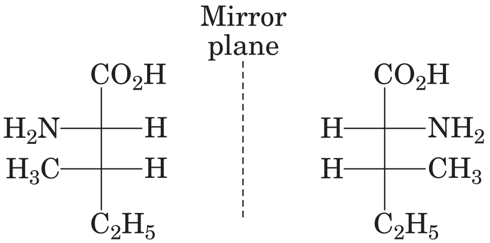
The D or L designation for an amino acid refers to the configuration of the α-carbon regardless of the number of chiral carbons in the molecule. Thus, L-threonine with two chiral carbons is the (2*S*, 3*R*) stereoisomer, while its enantiomer D-threonine is the (2*R*, 3*S*) stereoisomer. Similarly, L-isoleucine is the (2*S*, 3*S*) stereoisomer, while its enantiomer D-isoleucine is the (2*R*, 3*R*) stereoisomer.



L-Threonine
(2*S*,3*R*)-Threonine

D-Threonine
(2*R*,3*S*)-Threonine

;



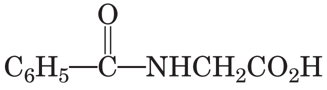
L-Isoleucine
(2*S*,3*S*)-Isoleucine

D-Isoleucine
(2*R*,3*R*)-Isoleucine

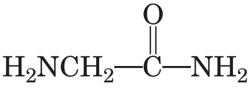
10.1.3 Amino Acids as Dipolar Ions

Although the amino acids are generally shown as containing an amino group and a carboxyl group, $H_2NCHRCO_2H$, certain physical and chemical properties are inconsistent with this structure. These are as follows:

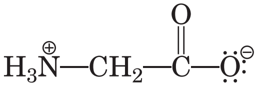
(i) In contrast to carboxylic acids and amines, the amino acids are nonvolatile crystalline solids which melt with decomposition at much higher temperatures. Glycine, for example, melts at 262°C (with decomposition), and tyrosine melts at 310°C (also with decomposition). *N*-Benzoylglycine or hippuric acid, a much larger molecule than glycine, and glycinamide, the amide of glycine, have much lower melting points. The former compound lacks the $—\ddot{N}H_2$ group and the latter compound lacks the —COOH group, and neither can exist as a zwitterion or dipolar ion.


$$C_6H_5—\overset{\overset{\displaystyle O}{\|}}{C}—NHCH_2CO_2H$$

N-Benzoylglycine (hippuric acid)
(mp 190°C)


$$H_2NCH_2—\overset{\overset{\displaystyle O}{\|}}{C}—NH_2$$

Glycinamide
(mp 68°C)


$$H_3\overset{\oplus}{N}—CH_2—\overset{\overset{\displaystyle O}{\|}}{C}—\ddot{\underset{\cdot\cdot}{O}}:^{\ominus}$$

Glycine
(mp 262°C)

(ii) They are appreciably soluble in water, but insoluble in non-polar solvents like benzene, ether, petroleum ether, etc.

The higher melting points and greater solubilities in water than in ether are characteristics expected of salts, not uncharged organic compounds. These saltlike characteristics are, however, what would be expected of zwitterionic compound. In the solid state of the amino acids, the strong electrostatic forces that result from the attraction between positive and negative charges on different molecules are much like those between the ions in a salt. The solid state is, therefore, stabilized by these attraction which resist conversion of the solid into a liquid (a pure liquid melt or solution). The best solvent for most amino acids is water and this is because it solvates the ionic groups by ion-dipole attraction and H-bonding.

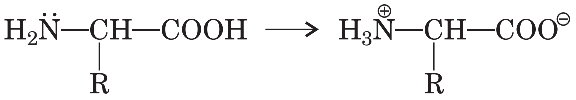
(iii) The dipole moments of the amino acids are very large. In fact, the values are much larger than those of similar-sized molecules with only one of the two functional groups. For example:

$H_3\overset{\oplus}{N}—CH_2—CO_2^{\ominus}$	$CH_3(CH_2)_3NH_2$	CH_3CH_2COOH
Glycine	Butylamine	Propanoic acid
(μ = 14 D)	(μ = 1·4 D)	(μ = 1·7 D)

A large dipole moment is expected for molecules containing a great deal of separated charge.

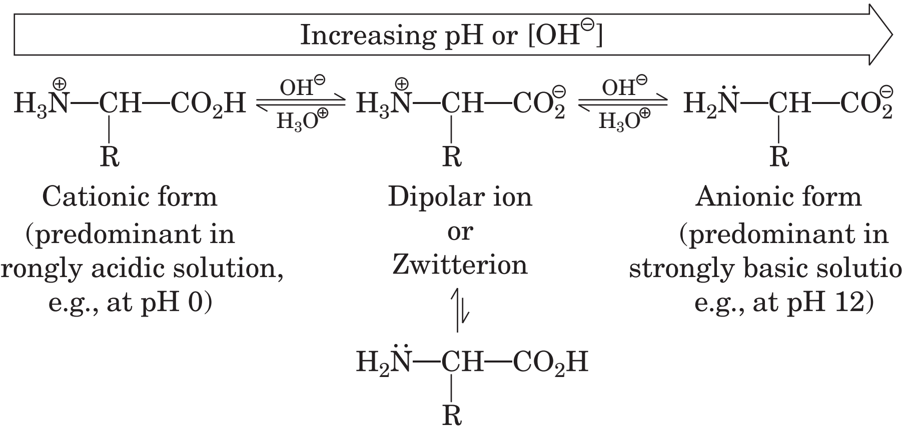
(iv) Acidity and basicity constants of amino acids are very much lower for —COOH and —NH_2 groups. The simplest amino acid glycine, for example, has $K_a = 1.6 \times 10^{-10}$ and $K_b = 2.5 \times 10^{-12}$, whereas most carboxylic acids have K_a values of about 10^{-5} and most aliphatic amines have K_b values of about 10^{-4}.

All these properties are very much consistent with a dipolar ion structure for the amino acids (Ia).



$$\underset{\text{I}}{H_2\ddot{N}—\underset{\substack{|\\R}}{CH}—COOH} \longrightarrow \underset{\text{Ia}}{H_3\overset{\oplus}{N}—\underset{\substack{|\\R}}{CH}—COO^{\ominus}}$$

When an amine is added to a carboxylic acid, an ammonium salt is obtained. This occurs by the transfer of a proton from the carboxyl group (—COOH) to the amino group (—NH_2). However, when both the groups form part of the same molecule as in the case of amino acids, the transfer of proton occurs intramolecularly to produce what is called a *dipolar ion* or *zwitter ion* or *inner salt*, a form in which the carboxyl group is present as a carboxylate ion, —$CO_2^{\ominus}$ and the amino group is present as an ammonium group, —$\overset{\oplus}{N}H_3$. Because amino acids contain both acidic (—$\overset{\oplus}{N}H_3$) and basic (—$CO_2^{\ominus}$) groups, they are amphoteric (possess both acidic and basic properties) i.e., they can accept a proton from a stronger acid as well as donate a proton to a stronger base. In aqueous solutions, the amino acids exist as the following species which are in equilibrium.



Increasing pH or [OH$^\ominus$]

$$H_3\overset{\oplus}{N}-\underset{R}{CH}-CO_2H \underset{H_3O^\oplus}{\overset{OH^\ominus}{\rightleftharpoons}} H_3\overset{\oplus}{N}-\underset{R}{CH}-CO_2^\ominus \underset{H_3O^\oplus}{\overset{OH^\ominus}{\rightleftharpoons}} H_2\ddot{N}-\underset{R}{CH}-CO_2^\ominus$$

Cationic form
(predominant in
strongly acidic solution,
e.g., at pH 0)

Dipolar ion
or
Zwitterion

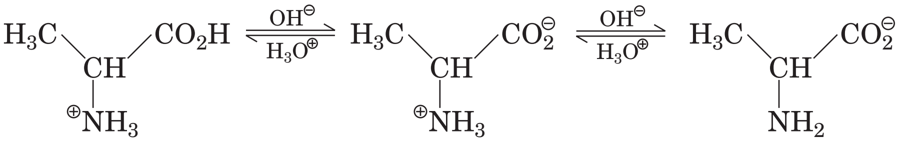
Anionic form
(predominant in
strongly basic solutions,
e.g., at pH 12)

$$\Updownarrow$$

$$H_2\ddot{N}-\underset{R}{CH}-CO_2H$$

Very small uncharged
form
(about 1 part in 10^5 parts)

The predominant form of the amino acid present in a solution actually depends on the pH of the solution and on the nature of the amino acid. Let us consider an amino acid, such as alanine, with a side chain that contains neither acidic nor basic groups. When alanine is dissolved in a strongly acidic solution (e.g., pH 0), the $-CO_2^\ominus$ group is protonated to a free $-CO_2H$ group, and the molecule then contains an overall positive charge, i.e., the amino acid exists mainly as a cation. Due to the –I effect of the $-\overset{\oplus}{N}H_3$ group, the pK_a value of this cationic acid is considerably lower (2.3) than the pK_a of the ordinary carboxylic acid (e.g., propanoic acid, pK_a = 4.89).



Cationic form
of alanine
(pK_{a1} = 2.3)

Dipolar ion or
Zwitterionic form
of alanine
(pK_{a2} = 9.7)

Anionic form
of alanine

When a base is added to the solution of the net cationic form of alanine, the first proton removed is the carboxylic acid proton. When a pH of 2.3 is reached the carboxylic acid proton will have been removed from half of the molecules, i.e., half of the cationic form will be converted to the dipolar ion. The pH represents the pK_a of the alanine carboxylic acid proton (denoted as pK_{a1}), as can be demonstrated by the **Henderson–Hasselbalch equation**.

[The Henderson–Hasselbalch equation may be represented as follows:

$$\mathrm{p}K_\mathrm{a} = \mathrm{pH} + \log\frac{[\mathrm{HA}]}{[\mathrm{A}^{\ominus}]}$$

Therefore, when the acid is half neutralized, i.e., when the concentration of acid, [HA], is equal to the concentration of its conjugate base, $[\mathrm{A}^{\ominus}]$, $\log\frac{[\mathrm{HA}]}{[\mathrm{A}^{\ominus}]} = \log 1 = 0$, and thus $\mathrm{pH} = \mathrm{p}K_\mathrm{a}$.]

As more base is added, i.e., the pH is raised further, alanine reaches its isoelectric point (p*I*) the pH at which all of alanine's carboxylic acid protons have been removed but not its aminium protons. The molecules then exist in electrically neutral (because the carboxylate group bears a –1 charge and the aminium group bears a +1 charge) zwitterionic form (dipolar ion). The p*I* of alanine is 6.0. As the pH is raised further by adding base, protons from the aminium ion will start to be removed, until at pH 9.7 half of the aminium group will have lost a proton. The pH represents the $\mathrm{p}K_\mathrm{a}$ of the aminium ($-\overset{\oplus}{\mathrm{N}}\mathrm{H}_3$) group. Finally, as the pH is further increased (e.g., pH = 14) by adding more base to the solution, the remaining aminium protons will be lost. At this point the molecules carry a net anionic charge from their $-\mathrm{CO}_2^{\ominus}$ group. The amino groups are now electrically neutral.

The following figure (Figure 10.1) shows a titration curve for these equilibria. The graph represents the change in pH as a function of the number of molar equivalent of alkali. Since alanine has two protons to lose in its net cationic form (the $-\overset{\oplus}{\mathrm{N}}\mathrm{H}_3$ proton and —COOH proton), when one molar equivalent of $\mathrm{OH}^{\ominus}$ has been added, the molecules will have each lost one proton and they will be electrically neutral dipolar ion.

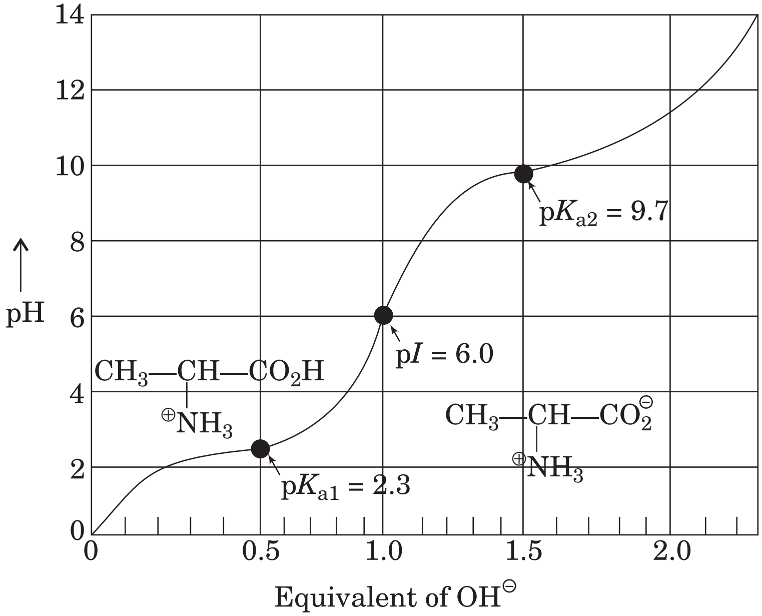


Figure 10.1 Titration curve for alanine hydrochloride

10.1.4 Isoelectric Points of Amino Acids

In an acidic solution (lower pH), an amino acid bears a positive charge and in a basic solution (higher pH), it bears a negative charge. In some intermediate pH, the concentration of the dipolar ion is at its maximum and the concentrations of the anion and cation are equal. This pH at which the total charge on all molecules of the amino acid is zero is called the **isoelectric pH or isoelectric point, p*I***. Each amino acid has a particular isoelectric point. When an electric current is passed through the aqueous solution of an amino acid at a pH lower than p*I*, the amino acid migrates towards the cathode because it exists mainly as a cation. Similarly, at a pH higher than p*I* it migrates towards the anode because it exists mainly as an anion. But at a pH equal to p*I* there occurs no net migration because the amino acid exists mainly as a zwitterion at this pH. Therefore, the isoelectric point may also be defined as the pH at which the amino acid does not migrate under the influence of an electric field.

10.1.4.1 The isoelectric point (pI) of any neutral amino acid is equal to half of the two pK_a values, one obtained as a conjugate acid (pK_{a1}) and the other as a dipolar ion (pK_{a2})

If the isoelectric amino acid is represented as $H_3\overset{\oplus}{N}—CHR—CO_2^{\ominus}$, we have the following equilibria:

$$\underset{\text{Conjugate acid (cA) of the amino acid}}{H_3\overset{\oplus}{N}—CHR—CO_2H} \rightleftharpoons \underset{\text{Dipolar ion}}{H_3\overset{\oplus}{N}—CHR—CO_2^{\ominus}} + H^{\oplus}$$

$$\underset{\text{Dipolar ion}}{H_3\overset{\oplus}{N}—CHR—CO_2^{\ominus}} \rightleftharpoons \underset{\text{Conjugate base (cB) of the amino acid}}{H_2N—CHR—CO_2^{\ominus}} + H^{\oplus}$$

$$\therefore \quad K_{al} = \frac{[\text{Dipolar ion}][H^{\oplus}]}{[cA]}; K_{a2} = \frac{[cB][H^{\oplus}]}{\text{Dipolar ion}}$$

At the isoelectric point (p*I*), the concentration of the dipolar ion is a maximum and since the net charge is zero,

$$[cA] = [cB]$$

$$\therefore \quad \frac{[\text{Dipolar ion}][H^{\oplus}]}{K_{a1}} = \frac{K_{a2}[\text{Dipolar ion}]}{[H^{\oplus}]}$$

$$\therefore \quad [H^{\oplus}]^2 = K_{a1}\,K_{a2}$$

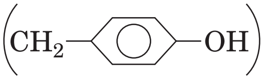
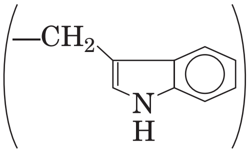
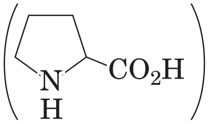
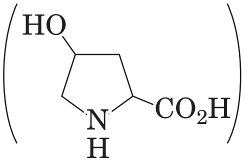
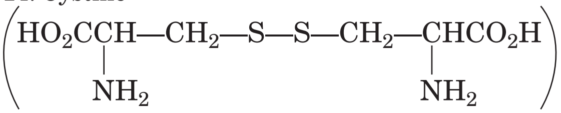
$$\therefore \quad -\log_{10}[H^{\oplus}]^2 = -\log_{10} K_{a1} - \log_{10} K_{a2}$$

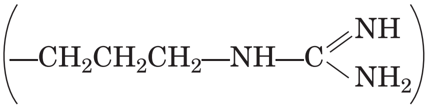
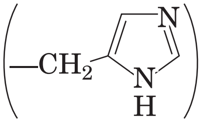
$$\therefore \quad 2pH = pK_{a1} + pK_{a2}$$

$$\therefore \quad pH = \frac{pK_{a1} + pK_{a2}}{2} = pI \text{ (the isoelectric point)}$$

It is to be noted that an isoelectric point of approximately 6 is typical for amino acids containing no additional acidic or basic groups on their side chains.

10.1.4.2 pK_{a1}, pK_{a2}, pK_{a3} (for acidic and basic side chain) and pI values of common naturally occurring amino acids are given in the following table.

A. Neutral Amino Acids (structure of —R)	**pK_{a1} (α-CO_2H)**	**pK_{a1} (α-$\overset{\oplus}{N}H_3$)**	**pK_{a3} (side chain)**	**pI**
1. Glycine	2.3	9.6	—	6.0
2. Alanine (—CH_3)	2.3	9.7		6.0
3. Valine (—$CHMe_2$)	2.3	9.6		6.0
4. Leucine (—CH_2CHMe_2)	2.4	9.6		6.0
5. Isoleucine (—CHMeEt)	2.4	9.7		6.1
6. Phenylalanine (—CH_2Ph)	1.8	9.1		5.5
7. Tyrosine 	2.2	9.1	10.1	5.7
8. Tryptophan 	2.4	9.4		5.9
9. Serine (—CH_2OH)	2.2	9.2		5.7
10. Threonine (—CHOHMe)	2.6	10.4		6.5
11. Proline  Complete structure	2.0	10.6		6.3
12. 4-Hydroxyproline  Complete structure	1.9	9.7		6.3
13. Cysteine (—CH_2SH)	1.7	10.8	8.3	5.0
14. Cystine  $\left(\underset{\displaystyle NH_2}{HO_2CCH}—CH_2—S—S—CH_2—\underset{\displaystyle NH_2}{CHCO_2H}\right)$ Complete structure	1.6 2.3	7.9 9.9		5.1
15. Methionine (—CH_2CH_2SMe)	2.3	9.2	5.8	
pI = (pK_{a1} + pK_{a2})/2				

B. Basic Amino Acids (Structure of —R)	**pK_{a1} (α-CO_2H)**	**pK_{a2} (α-$\overset{\oplus}{N}H_3$)**	**pK_{a3} (Side chain)**	**p*I***
16. Lysine (—$CH_2CH_2CH_2CH_2NH_2$)	2.2	9.0	10.5	9.8
17. Arginine 	2.2	9.0	12.5	10.8
18. Histidine 	1.8	9.2	6.0	7.6

p*I* = (pK_{a2} + pK_{a3})/2 (average of the two *highest* pK_a values)

C. Acidic Amino Acids	**pK_{a1} (α-CO_2H)**	**pK_{a2} (α-$\overset{\oplus}{N}H_3$)**	**pK_{a3} (Side chain)**	**p*I***
19. Aspartic acid (—CH_2CO_2H)	2.1	9.8	3.9	3.0
20. Glutamic acid (—$CH_2CH_2CO_2H$)	2.2	9.7	4.3	3.2
21. Asparagine (—CH_2CONH_2)	2.0	8.8		5.4
22. Glutamine (—$CH_2CH_2CONH_2$)	2.2	9.1		5.7

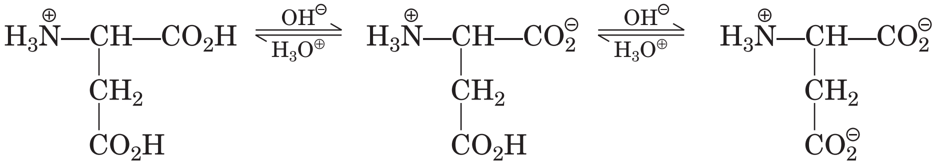
p*I* = (pK_{a1} + pK_{a2})/2 (average of the two *lowest* pK_a values)

10.1.4.3 Isoelectric points (pI) of neutral, acidic and basic amino acids:

(i) *The isoelectric point (pI) of a monoamino monocarboxylic acid lies somewhat on the acid side of neutrality (pH 7).* A monoamino monocarboxylic acid, $H_3\overset{\oplus}{N}CHRCO_2^{\ominus}$, is somewhat more acidic than basic (the K_a and K_b values of glycine, for example are 1.6×10^{-10} and 2.5×10^{-12}, respectively). When crystals of such an acid are added to water, the resulting solution contains more of the anionic form II, $H_2NCHRCO_2^{\ominus}$, than of the cationic form III, $H_3\overset{\oplus}{N}CHRCO_2H$. This "excess" ionization of the aminium ion to amine (I $\rightleftharpoons$ II + $H^{\oplus}$) must be repressed, by addition of acid, to reach the isoelectric pH or isoelectric point, which therefore lies somewhat on the acid side of neutrality (pH 7). The isoelectric point of glycine, for example, is at pH 6.0.

$$\underset{\substack{\text{II}\\ \text{Anionic form}}}{H_2NCHRCO_2^{\ominus}} \underset{OH^{\ominus}}{\overset{H_3O^{\oplus}}{\rightleftharpoons}} \underset{\substack{\text{I}\\ \text{Dipolar ion}}}{H_3\overset{\oplus}{N}CHRCO_2^{\ominus}} \underset{OH^{\ominus}}{\overset{H_3O^{\oplus}}{\rightleftharpoons}} \underset{\substack{\text{III}\\ \text{Cationic form}}}{H_3\overset{\oplus}{N}CHRCO_2H}$$

(ii) *The isoelectric point of a monoamino dicarboxylic acid lies on the acid side of neutrality.* A monoamino dicarboxylic acid such as aspartic acid is also more acidic than basic (K_a for the extra —CO_2H group is 10^{-5} and K_b is 10^{-12}). If crystals of aspartic acid are added to water, the resulting solution contains more of the anionic form III, than of the cationic form II.



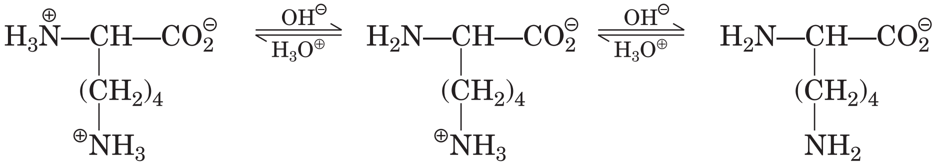
II Cationic form

I Dipolar ion of aspartic acid

III Anionic form

The “excess” ionization of the $–CO_2H$ group to $—CO_2^{\ominus}$ ($I \rightleftharpoons III + H^{\oplus}$) must be repressed by addition of acid, to reach the isoelectric pH or isoelectric point, which therefore lies on the acid side of neutrality (pH 7). For aspartic acid, for example, the isoelectric point is at pH 3.0.

(iii) *The isoelectric point of a diamino monocarboxylic acid lies on the basic side of neutrality.* A diamino monocarboxylic acid like lysine is somewhat basic than acidic. When some crystals of lysine are added to water, the resulting solution contains more of the cationic form II and than the anionic form III.



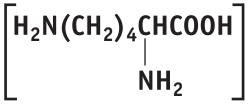
II Cationic form

I Dipolar ion of Lysine

III Anionic form

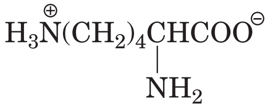
This ‘excess’ protonation of $—NH_2$ to $—\overset{\oplus}{N}H_3$ ($I + H^{\oplus} \rightleftharpoons II$) must be repressed, by addition of base, to reach the isoelectric point, which therefore lies somewhat on the basic side of neutrality (pH 7). For lysine, for example, the isoelectric point is at pH 9.8.

10.1.3.4 Possible dipolar structures for (a) lysine, (b) aspartic acid, (c) arginine and (d) tyrosine and prediction of the actual structure in each case.

(a) Lysine 

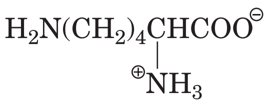
$$\left[H_2N(CH_2)_4\underset{NH_2}{\underset{|}{C}}HCOOH\right]$$

Of the two possible dipolar structures of the basic amino acid Lysine (I and II), I is the actual structure because the more distant ε-amino group is less affected by the electron-attracting and hence base-weakening —COOH group and as a consequence, it becomes more basic and preferably takes up the proton.



$$\mathrm{H_3\overset{\oplus}{N}(CH_2)_4\underset{NH_2}{\underset{|}{C}}HCOO^{\ominus}}$$

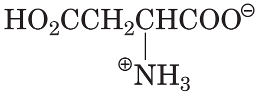
I
(actual dipolar structure
of lysine)



$$\mathrm{H_2N(CH_2)_4\underset{^{\oplus}NH_3}{\underset{|}{C}}HCOO^{\ominus}}$$

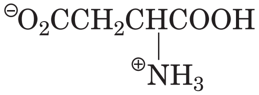
II

(b) Aspartic acid $\left(\mathrm{HO_2CCH_2\underset{NH_2}{\underset{|}{C}}HCOOH}\right)$ I and II are the two possible dipolar structures of aspartic acid. I is the actual structure because the nearer —COOH group is more affected by the electron-attracting and hence acid-strengthening —NH_2 group and consequently, it becomes more acidic and loses proton.



$$\mathrm{HO_2CCH_2\underset{^{\oplus}NH_3}{\underset{|}{C}}HCOO^{\ominus}}$$

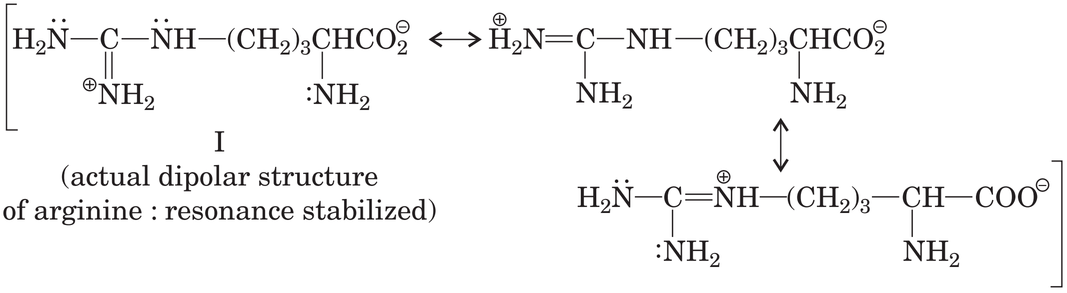
I
(actual dipolar structure
of aspartic acid)



$$\mathrm{^{\ominus}O_2CCH_2\underset{^{\oplus}NH_3}{\underset{|}{C}}HCOOH}$$

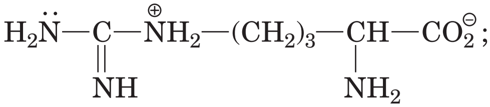
II

(c) Arginine $\left[\mathrm{H_2N-\underset{NH}{\underset{\|}{C}}-NH(CH_2)_3\underset{NH_2}{\underset{|}{C}}HCO_2H}\right]$ Of the four possible dipolar structures of arginine (I, II, III and IV), I is the actual structure. This is because the double bonded nitrogen is the most basic since the conjugate acid corresponding to it is a resonance-stabilized cation.

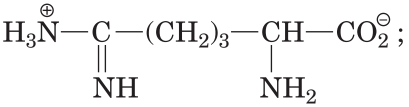


$$\left[\mathrm{H_2\ddot{N}-\underset{^{\oplus}NH_2}{\underset{\|}{C}}-\ddot{N}H-(CH_2)_3\underset{:NH_2}{\underset{|}{C}}HCO_2^{\ominus}} \longleftrightarrow \mathrm{H_2\overset{\oplus}{N}{=}\underset{NH_2}{\underset{|}{C}}-NH-(CH_2)_3\underset{NH_2}{\underset{|}{C}}HCO_2^{\ominus}} \longleftrightarrow \mathrm{H_2\ddot{N}-\underset{:NH_2}{\underset{|}{C}}{=}\overset{\oplus}{N}H-(CH_2)_3-\underset{NH_2}{\underset{|}{CH}}-COO^{\ominus}}\right]$$

I
(actual dipolar structure
of arginine : resonance stabilized)



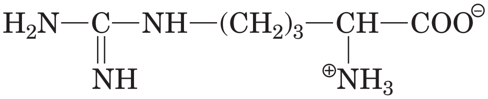
$$\mathrm{H_2\ddot{N}-\underset{NH}{\underset{\|}{C}}-\overset{\oplus}{N}H_2-(CH_2)_3-\underset{NH_2}{\underset{|}{CH}}-CO_2^{\ominus}};$$



$$\mathrm{H_3\overset{\oplus}{N}-\underset{NH}{\underset{\|}{C}}-(CH_2)_3-\underset{NH_2}{\underset{|}{CH}}-CO_2^{\ominus}};$$

II

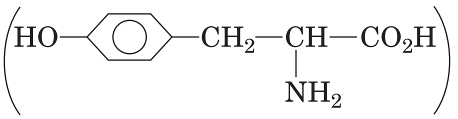
III



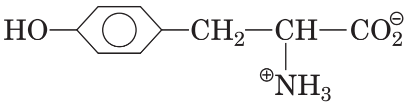
$$\mathrm{H_2N-\underset{NH}{\underset{\|}{C}}-NH-(CH_2)_3-\underset{^{\oplus}NH_3}{\underset{|}{CH}}-COO^{\ominus}}$$

IV

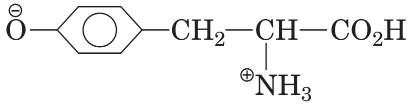
(d) Tyrosine



Of the two possible dipolar structures of tyrosine (I and II), I is the actual structure because the —COOH group ($K_a \simeq 10^{-3}$) is much more acidic than a phenolic —OH group ($K_a \simeq 10^{-10}$), and so, loses the proton preferably.



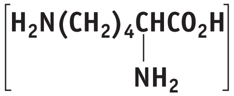
I
(actual dipolar structure
of tyrosine)



II

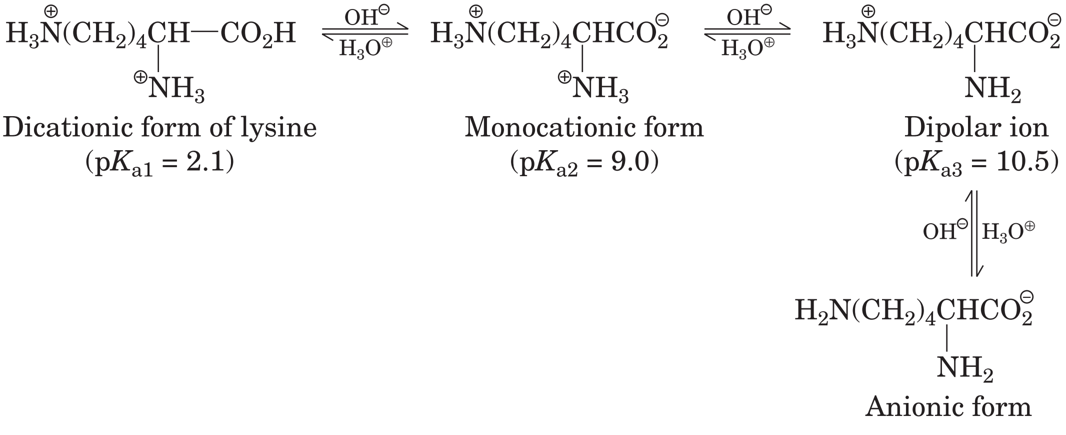
10.1.4.4 Behaviour of lysine (a basic amino acid) and aspartic acid (an acidic amino acid) as the pH values of their strongly acidic solution are generally raised by adding a base (e.g., $OH^{\ominus}$) and calculation of their isoelectric points (pI) using their pK_a values.

Lysine



$$\left[H_2N(CH_2)_4\underset{\displaystyle NH_2}{\underset{|}{C}}HCO_2H\right]$$

Lysine has an extra —NH_2 group at the terminal carbon of its side chain. In strongly acidic solution, lysine will exist as a dication because both of the —NH_2 groups will undergo protonation. As the pH of the solution is raised by the addition of base, the proton of the carboxyl group (pK_a = 2.1) is to be lost first. The next proton to be lost is from the α-aminium group (pK_a = 9.0) and the last is from the ε-aminium group (pK_a = 10.5).



Dicationic form of lysine
(pK_{a1} = 2.1)

Monocationic form
(pK_{a2} = 9.0)

Dipolar ion
(pK_{a3} = 10.5)

Anionic form

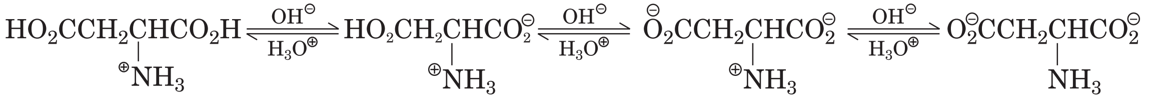
The isoelectric point (pI) of lysine is the average of its two highest pK_a values, i.e., the average of pK_{a2} (the monocation) and pK_{a3} (the dipolar ion) and this is because the species with zero total charge exists primarily between pH 9.0 and 10.5 which are pK_{a2} and pK_{a3} respectively.

$$\therefore \qquad pI = \frac{9.0 + 10.5}{2} = 9.8$$

The pK_{a1}, i.e., the pK_a of the —COOH group, does not enter the picture because neither of the equilibria involving the dipolar ion involves ionization of the —CO_2H group.

Aspartic acid ($HO_2CCH_2\underset{\underset{NH_2}{|}}{CH}CO_2H$) Aspartic acid has an extra —CO_2H group on its side chain.

In strongly acidic solution, aspartic acid will exist in the cationic form. The first proton to be lost as the pH is raised by addition of base is the proton of the α-CO_2H group and this is because it is relatively more acidic (nearer to the electron-attracting $—\overset{\oplus}{N}H_3$ group). The next proton to be lost is from the side chain —COOH group and the last is from the $\alpha–\overset{\oplus}{N}H_3$ group.



$$HO_2CCH_2\underset{\underset{^{\oplus}NH_3}{|}}{C}HCO_2H \underset{H_3O^{\oplus}}{\overset{OH^{\ominus}}{\rightleftharpoons}} HO_2CH_2\underset{\underset{^{\oplus}NH_3}{|}}{C}HCO_2^{\ominus} \underset{H_3O^{\oplus}}{\overset{OH^{\ominus}}{\rightleftharpoons}} \overset{\ominus}{O}_2CCH_2\underset{\underset{^{\oplus}NH_3}{|}}{C}HCO_2^{\ominus} \underset{H_3O^{\oplus}}{\overset{OH^{\ominus}}{\rightleftharpoons}} O_2^{\ominus}CCH_2\underset{\underset{NH_3}{|}}{C}HCO_2^{\ominus}$$

Cationic form of aspartic acid ($pK_{a1} = 2.1$)

(Dipolar ion ($pK_{a2} = 3.9$)

Monocationic form ($pK_{a3} = 9.8$)

Dianionic form

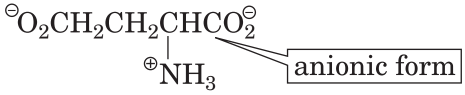
The isoelectric point (pI) of aspartic acid is the average of its two lowest pK_a values, i.e., the average of pK_{a1} (the cationic form) and pK_{a2} (the dipolar ion) and this is because the species with zero total charge exists primarily between pH 2.1 and 3.9, which are pK_{a1} and pK_{a2}, respectively.

$$\therefore \qquad pI = \frac{2.1 + 3.9}{2} = 3.0$$

The pK_{a3} of aspartic acid, i.e., the pK_a of the $\alpha–\overset{\oplus}{N}H_3$ group does not enter the picture because neither of the equilibria involving the dipolar ion involves deprotonation of the $\alpha–\overset{\oplus}{N}H_3$ group.

10.1.4.5 To predict the form in which the amino acids (a) glutamic acid (b) histidine (c) tyrosine and (d) arginine exist predominantly at physiological pH (i.e., pH = 7.3).

(a) Glutamic acid Since the value of physiological pH (the pH that exists in the cells and fluids of living organisms) is greater than the pK_a values of both the carboxyl groups of glutamic acid (2.2 and 4.3), these groups remain in their basic forms. However, because this pH is less than the pK_a of the protonated amino group (9.9), this group remains in its acidic form. Therefore, the form in which glutamic acid exists predominantly at pH 7.3, the physiological pH, is as follows:

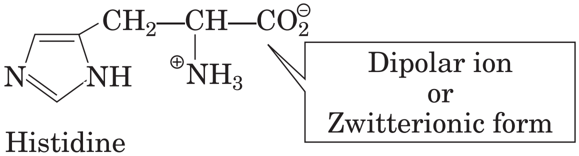


$${}^{\ominus}O_2CH_2CH_2\underset{\substack{| \\ {}^{\oplus}NH_3}}{CH}CO_2^{\ominus}$$

anionic form

Glutamic acid
(at physiological pH)

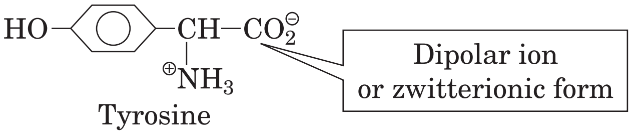
(b) Histidine The physiological pH is greater than the pK_a of the carboxyl group (1.8) and that of the protonated imidazole ring (6.0) of histidine. Therefore, these groups remain in their basic forms. Since the physiological pH is less than the pK_a of the aminium group, —$\overset{\oplus}{N}H_3$ (9.2), this group remains in its acidic form. Therefore, the form in which histidine exists predominantly at the physiological pH is as follows:



Dipolar ion
or
Zwitterionic form

Histidine
(at physiological pH)

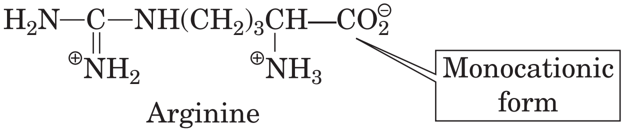
(c) Tyrosine Since the physiological pH is greater than the pK_a of the carboxyl group (2.2) of tyrosine, this group remains in the basic form. However, because this pH is less than the pK_a values of the aminium group, —$\overset{\oplus}{N}H_3$ (9.1) and the phenolic —OH group (10.1), these two groups remain in their acidic forms. Hence, the form in which tyrosine exists predominantly at the physiological pH (7.3) is as follows:



Dipolar ion
or zwitterionic form

Tyrosine
(at physiological pH)

(d) Arginine Because the physiological pH is greater than the pK_a of the carboxyl group (2.2) of arginine, the group remains in its basic form. However, the aminium group (—$\overset{\oplus}{N}H_3$) and the protonated guanidino group remain in their acidic forms because the physiological pH is less than their pK_a values. Therefore, the form in which arginine exists predominantly at the physiological pH (7.3) is as follows:



$$H_2N\text{—}\underset{\substack{\| \\ {}^{\oplus}NH_2}}{C}\text{—}NH(CH_2)_3\underset{\substack{| \\ {}^{\oplus}NH_3}}{CH}\text{—}CO_2^{\ominus}$$

Monocationic
form

Arginine
(at physiological pH)

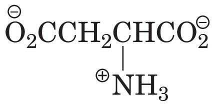
10.1.5 Electrophoresis

Electrophoresis is a method for separation and purification that depends on the movement of charged particles in an electric field. Differences in isoelectric point (p*I*) can be used to separate mixtures of amino acids by electrophoresis and this is because depending on isoelectric point amino acids may exist as neutral, positively charged or negatively charged species in a buffer solution having a particular pH.

When a few drops of a solution of amino acid mixture are placed in the centre of a piece of filter paper or in the centre of a layer of acrylamide gel and the paper or the gel is placed in a buffer solution between two electrodes and an electric field is applied, an amino acid with a p*I* greater than the pH of the solution must possess an overall positive charge and will migrate toward the cathode (the negative electrode). The farther the p*I* of the amino acid from the pH of the buffer solution, the more positive the amino acid will be and the farther it will migrate towards the cathode in a given amount of time. An amino acid with a p*I* less than the pH of the buffer will have an overall negative charge and will migrate toward the anode (the positive electrode). An amino acid with a p*I* equal to the pH of the buffer solution has no net charge (because it exists as a dipolar ion or zwitterion), so it does not move. If the two molecules possess the same charge, the large one will move slowly during electrophoresis because the same charge has to move with a greater mass.

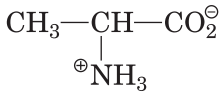
Let us consider a mixture of alanine, lysine, and aspartic acid. When this mixture is subjected to electrophoresis in a buffer that matches the isoelectric point of alanine (pH = 6.0). In this case, aspartic acid (p*I* = 2.8) which remains in the anionic form (because pH 6 is less acidic than its p*I*) migrates towards the positive electrode (the anode), alanine which exists in dipolar zwitterionic form with zero net charge remains at the origin, i.e., migrates towards neither of the electrodes, and lysine (p*I* = 9.7), which remains in the cationic form (because pH 6 is more acidic than its p*I*), migrates towards the negative electrode (the cathode). After a period of time, the separated amino acids are recovered by cutting the paper or scraping the bands out of the gel.

Structures of the three amino acids at pH 6:



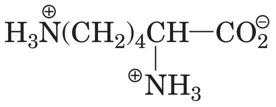
$$\overset{\ominus}{O}_2CCH_2\underset{\overset{|}{^{\oplus}NH_3}}{C}HCO_2^{\ominus}$$

Aspartic acid
(monoanion : charge –1)



$$CH_3-\underset{\overset{|}{^{\oplus}NH_3}}{CH}-CO_2^{\ominus}$$

Alanine
(neutral : charge 0)



$$H_3\overset{\oplus}{N}(CH_2)_4\underset{\overset{|}{^{\oplus}NH_3}}{CH}-CO_2^{\ominus}$$

Lysine
(monocation : charge +1)

When electrophoresis is used as analytical technique, i.e., to identify the amino acids present in the mixture, the paper or the acylamide gel is sprayed with nintydrin and then dried in a warm oven. Most of the amino acids form a purple product with ninhydrin. The number of different kinds of amino acids in the mixture is determined by the number of coloured spots on the filter paper or gel. The individual amino acids are then identified by comparing their locations on the paper or gel with those of standards. The following figure (Figure 10.2) shows the application of electrophoresis to the separation of aspartic acid, alanine, and lysine according to their charge type at a pH corresponding to the isoelectric point (p*I*) of alanine.

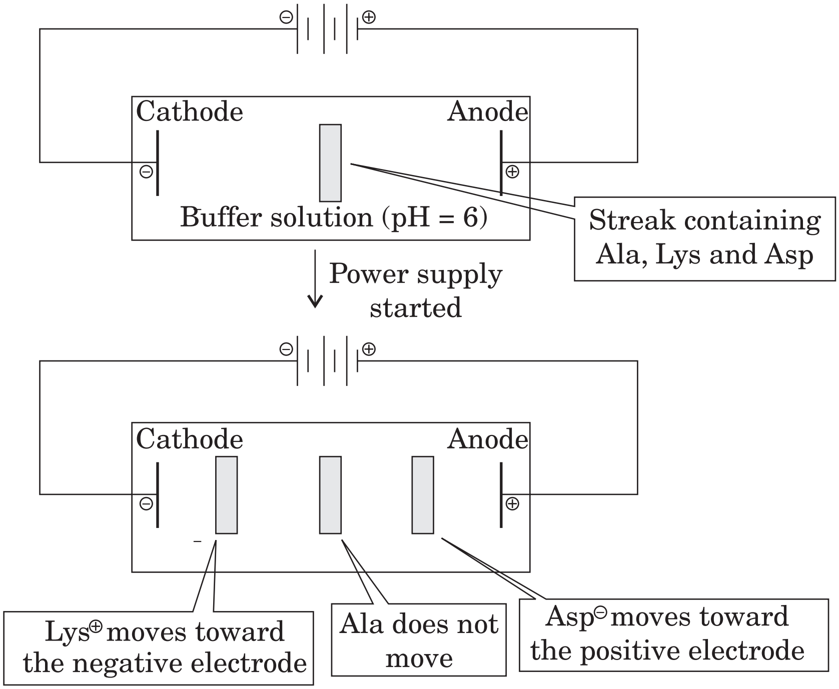

Cathode
Anode
Buffer solution (pH = 6)
Streak containing Ala, Lys and Asp
Power supply started
Cathode
Anode
Lys⊕ moves toward the negative electrode
Ala does not move
Asp⊖ moves toward the positive electrode

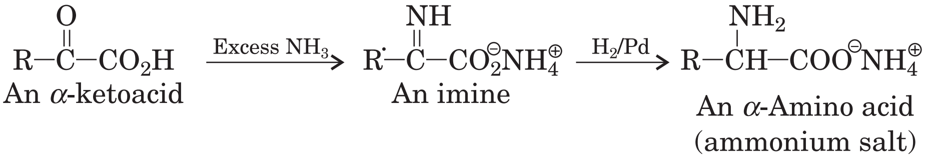
Figure 10.2 Separation of lysine, alanine and asparsic acid by electrophoresis

Electrophoresis is used mainly to analyze mixture of peptides and proteins, rather than individual amino acids. Because they consist of different numbers of amino acids and because they have different side chains, two peptides will have slightly different acid-base properties and slightly different net charges at a particular pH of the buffer used. Therefore, their mobilities in an electric field will be different, and electrophoresis can be used for their separation. The medium used to separate peptides and proteins is a polyacrylamide gel. So, this technique is called **gel electrophoresis**.

10.1.6 Synthesis of Amino Acids

Naturally occurring amino acids can be obtained by hydrolyzing proteins and then separating the amino acid mixture. Nevertheless, it is often less expensive to synthesize pure amino acids. When an unusual amino acid or an unnatural enantiomer is required, it must be synthesized. A number of methods for preparing amino acids are discussed below:

(i) Reductive Amination of α-Ketoacids When an α-Ketoacid is treated with ammonia, the ketone reacts to form an imine. The imine is reduced to an amine by hydrogen and palladium catalyst. Under these conditions, the —COOH group is not reduced.



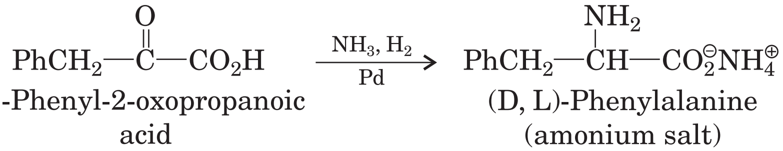
$$R-\overset{O}{\overset{\|}{C}}-CO_2H \xrightarrow{\text{Excess } NH_3} R-\overset{NH}{\overset{\|}{C}}-CO_2^{\ominus}NH_4^{\oplus} \xrightarrow{H_2/Pd} R-\overset{NH_2}{\overset{|}{C}H}-COO^{\ominus}NH_4^{\oplus}$$

An α-ketoacid

An imine

An α-Amino acid (ammonium salt)

Racemic phenylalanine, for example, can be synthesized by reductive amination of 3-phenyl-2-oxopropanoic acid.

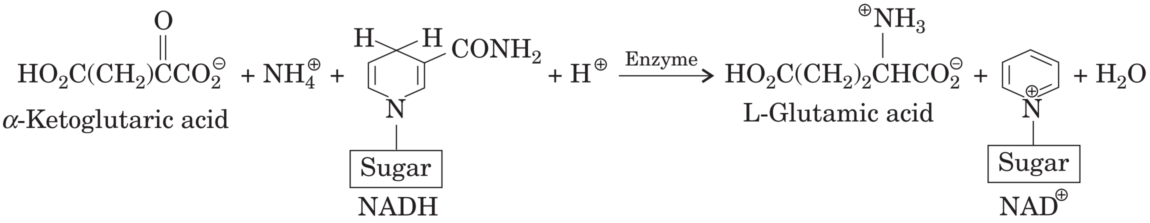


$$PhCH_2-\overset{O}{\overset{\|}{C}}-CO_2H \xrightarrow[Pd]{NH_3,\ H_2} PhCH_2-\overset{NH_2}{\overset{|}{C}H}-CO_2^{\ominus}NH_4^{\oplus}$$

3-Phenyl-2-oxopropanoic acid

(D, L)-Phenylalanine (amonium salt)

The biosynthesis of amino acids begins with reductive amination of α-ketoglutaric acid (a metabolic intermediate). The product of this enzyme-catalyzed reaction involving ammonium ion (the aminating agent) and NADH (the reducing agent) is pure L-glutamic acid and this is because the reduction occurs exclusively from the *Re* face of the imine.



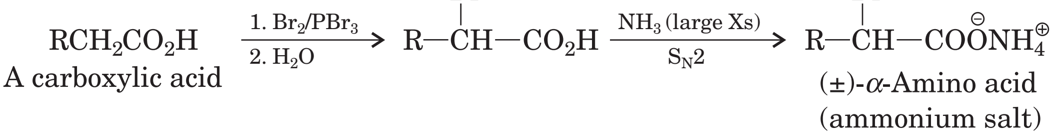
α-Ketoglutaric acid

NADH
(The reduced form of
nicotinamide adenine dinucleotide)

L-Glutamic acid

NAD⊕

(ii) Amination of α-halo acids The Hell-Volhard-Zelinsky (HVZ) reaction is an effective method for introducing bromine at the α position of a carboxylic acid. The resulting α-bromo acid is converted to a racemic α-amino acid by direct amination, using a large excess of ammonia (an S_N2 reaction).

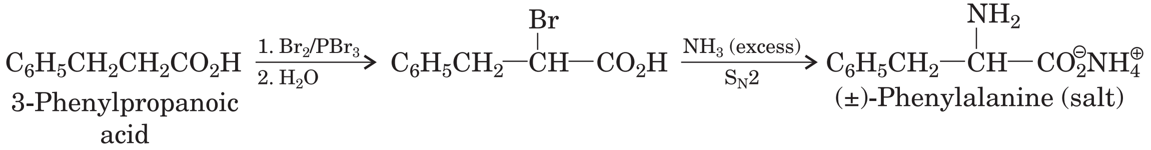


$$RCH_2CO_2H \xrightarrow[2.\ H_2O]{1.\ Br_2/PBr_3} R-\overset{Br}{\overset{|}{C}H}-CO_2H \xrightarrow[S_N2]{NH_3\ (\text{large Xs})} R-\overset{Br}{\overset{|}{C}H}-CO\overset{\ominus}{O}NH_4^{\oplus}$$

A carboxylic acid

(±)-α-Amino acid (ammonium salt)

Racemic phenylalanine, for example, can be prepared by bromination of 3-phenylpropanoic acid by the HVZ reaction followed by displacement (S_N2) bromide ion.



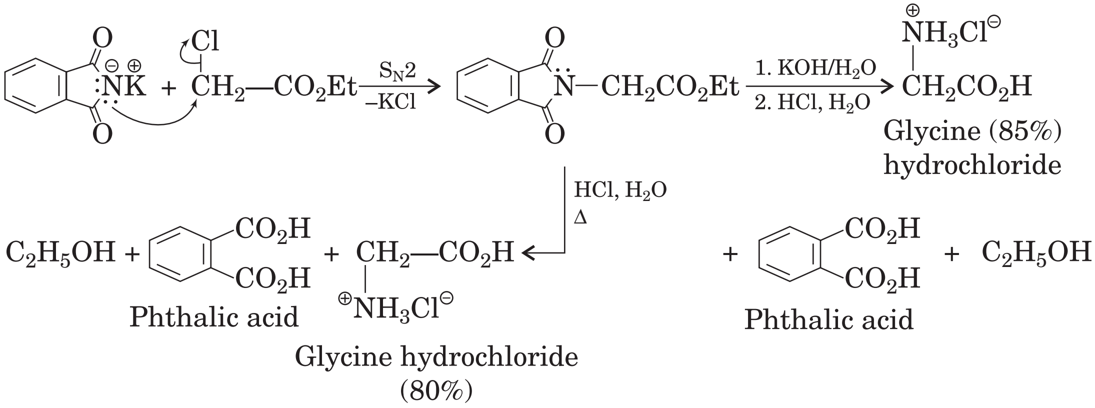
$$C_6H_5CH_2CH_2CO_2H \xrightarrow[2.\ H_2O]{1.\ Br_2/PBr_3} C_6H_5CH_2-\overset{\overset{\displaystyle Br}{|}}{C}H-CO_2H \xrightarrow[S_N2]{NH_3\ (excess)} C_6H_5CH_2-\overset{\overset{\displaystyle NH_2}{|}}{C}H-CO_2^{\ominus}NH_4^{\oplus}$$

3-Phenylpropanoic acid

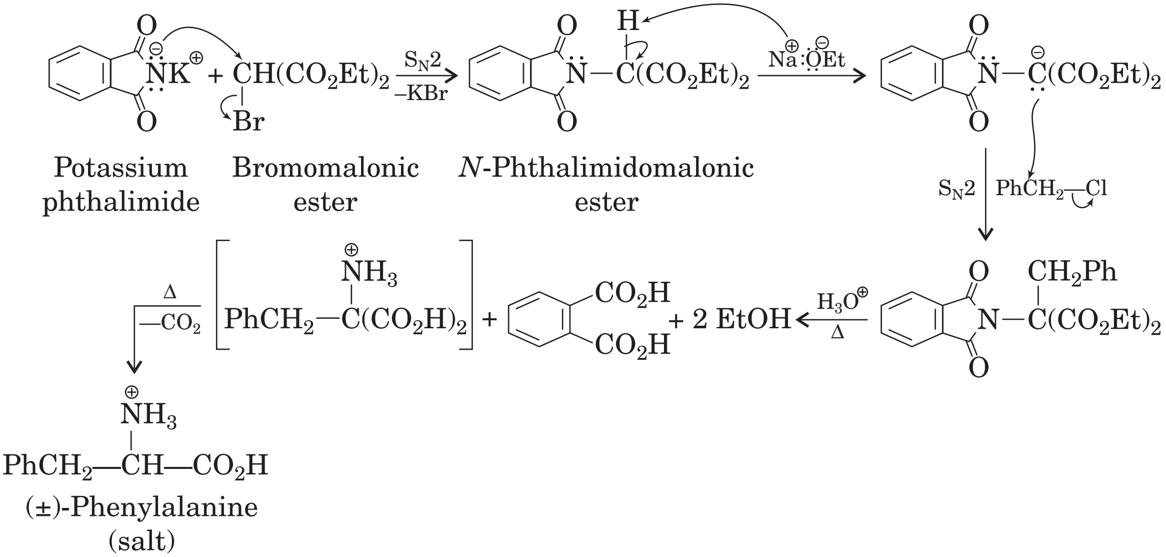
(±)-Phenylalanine (salt)

Because of overalkylation, alkylation of ammonia is not a good method for preparing 1° amines. However, use of a large excess of NH_3 in amino acid synthesis favours monoalkylation. Furthermore, amino acids are less reactive toward alkylating agent than simple alkylamines because the amino groups of amino acids are less basic (by about 0.8 pK_a unit) and therefore, less nucleophilic, than ammonia and simple amines. Also, branching in R-groups in amino acids provides a steric hindrance to further alkylation.

(iii) Gabriel phthalimide synthesis This method is, in fact, a modification of Gabriel synthesis of primary amines. The potassium salt of phthalimide is first allowed to react with an α-haloester. The resulting compound on acidic hydrolysis or alkaline hydrolysis followed by acidification produces phthalic acid and the α-amino acid. Glycine, for example, can be synthesized as follows:

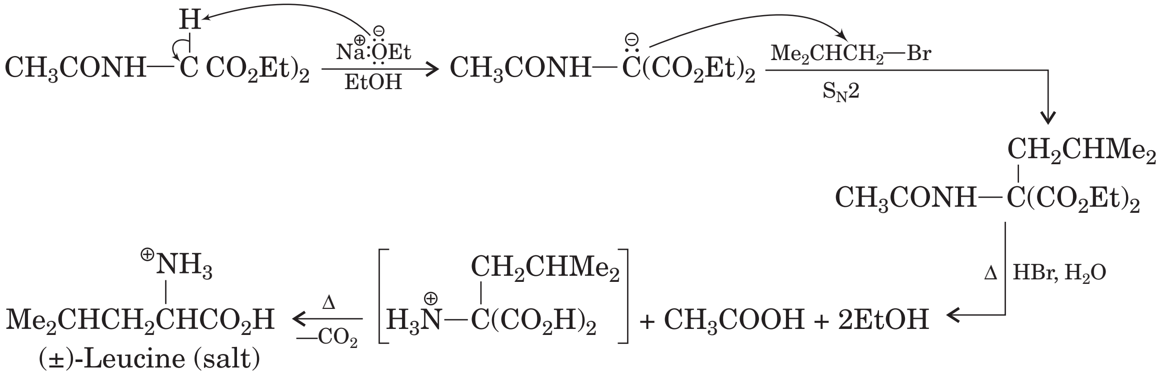


(iv) Gabriel–Malonic ester synthesis or N-phthalimidomalonic ester synthesis This is, in fact, a variation of the malonic ester synthesis which is quite useful for synthesizing α-amino acids. In this method, potassium phthalimide is first allowed to react with bromomalonic ester. An S_N2 reaction occurs to yield *N*-phthalimidomalonic ester. When this ester is treated with a strong base (sodium ethoxide), a resonance stabilized carbanion is obtained. The anion, in turn, is treated with an alkyl halide to give an alkylated product. Vigorous hydrolysis of this alkylated product causes hydrolysis of both the ester groups and the phthalimido group. Under these conditions the malonic acid derivative undergoes decarboxylation to yield an α-amino acid. Phenylalnine, for example, can be synthesized as follows:



The hydrolysis (in step 4) may also be carried out by alkali.

(v) Acetamidomalonic ester synthesis This widely used method is also a variation of the malonic ester synthesis. The malonic ester derivative used in this synthesis is acetamidomalonic ester or diethyl acetamidomalonate in which a protected amino group is already in place. This compound is treated with the strong base sodium ethoxide in ethanol to form the corresponding enolate ion. The enolate ion is then alkylated with an alkyl halide and the resulting compound is then heated with aqueous HCl or HBr. This causes the acetamido ($CH_3CONH—$) and ester groups to undergo hydrolysis to yield a malonic acid derivative. This dicarboxylic acid undergoes decarboxylation under the reaction conditions to give an α-amino acid. Leucine, for example, can be synthesized by this method as follows:



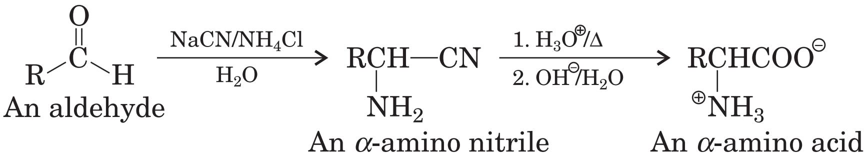
The hydrolysis in step 3 may also be carried out by alkali.

[Acetamidomalonic ester can be prepared as follows:

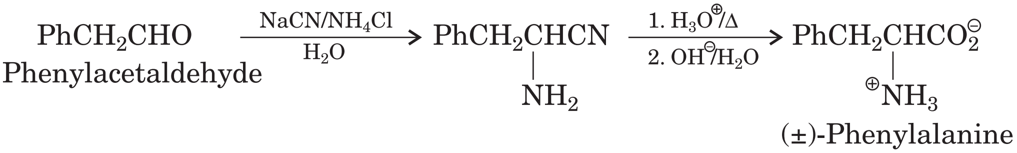
$$CH_2(CO_2Et)_2 \xrightarrow{HNO_2} O{=}N{-}CH(CO_2Et)_2 \rightarrow HO{-}N{=}C\,CO_2Et)_2 \xrightarrow[Ac_2O]{H_2/Pt} CH_3CONHCH(CO_2Et)_2$$

when malonic ester is treated with nitrous acid, a nitroso derivative is obtained. This undergoes ready tautomerization (nitroso-oxime tautomerism) to give the corresponding oxime. Hydrogenation of the oxime in acetic anhydride solution gives acetamidomalonic ester.]

(vi) Strecker Synthesis When an aldehyde is treated with an aqueous solution of ammonium chloride and sodium cyanide (a mixture equivalent to ammonium cyanide or NH_3 and HCN), an α-amino nitrile is obtained. When the resulting α-amino nitrile is hydrolyzed, an α-amino acid is obtained. This process for synthesizing α-amino acids is called the strecker synthesis.



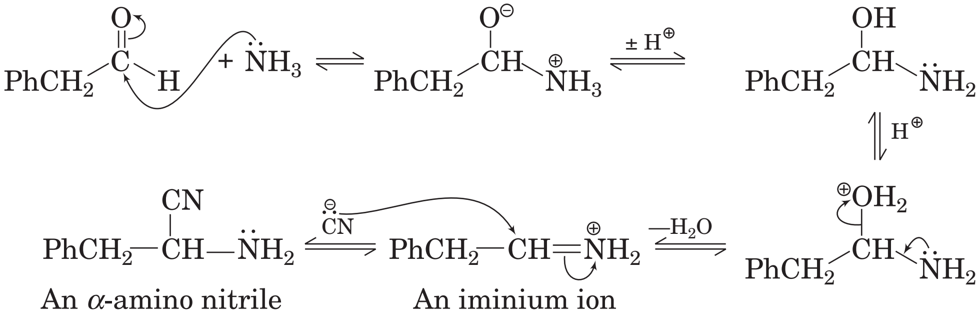
Phenylalanine, for example, can be prepared as follows:



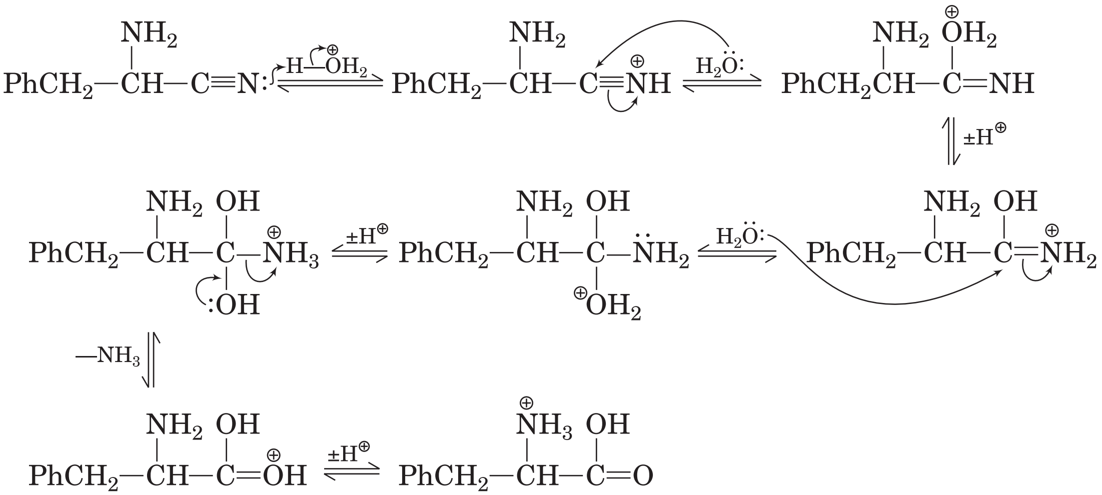
Mechanism:

$$NH_4Cl + NaCN \rightleftharpoons NH_4CN + NaCl\ ;\ NH_4Cl \rightleftharpoons NH_3 + HCN$$

Formation of α-amino nitrile:



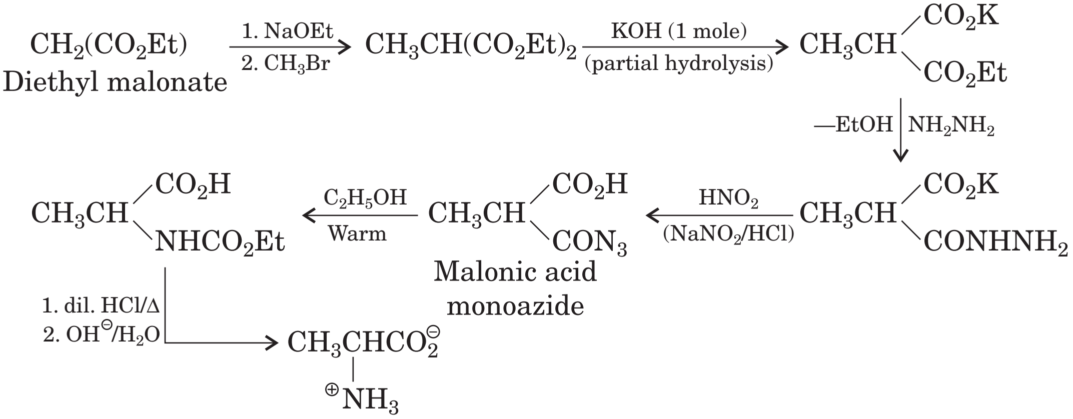
Hydrolysis of α-amino nitrile:



(±)-Phenylalanine (salt)

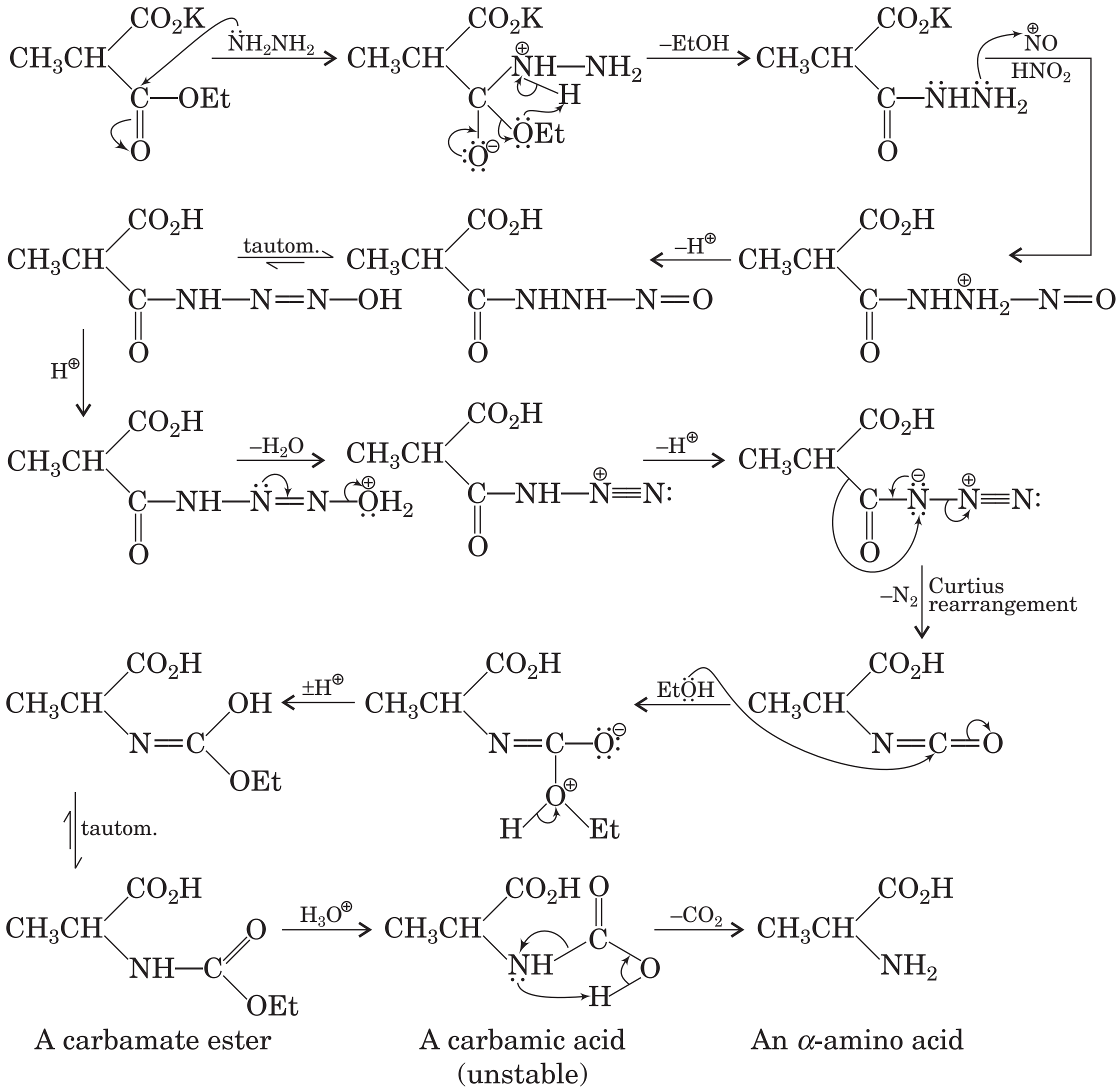
(vii) Methods involving the Curtius Rearrangement

(a) When malonic acid monoazide, prepared from diethyl malonate by a sequence of reactions, is warmed in the presence of ethanol, it undergoes the Curtius rearrangement to yield a carbamate ester. This ester on acidic hydrolysis produces an α-amino acid. Alanine, for example, can be prepared as follows:

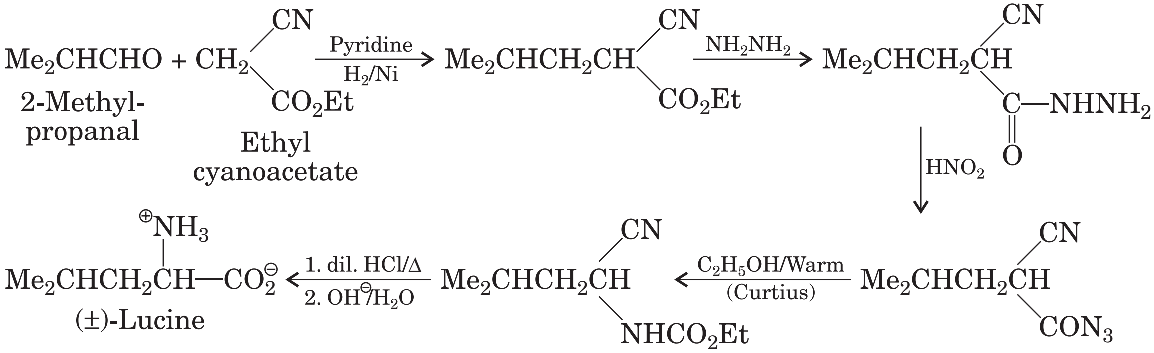


(±)-Alanine

*** Mechanism (Step 3–Step 6):**

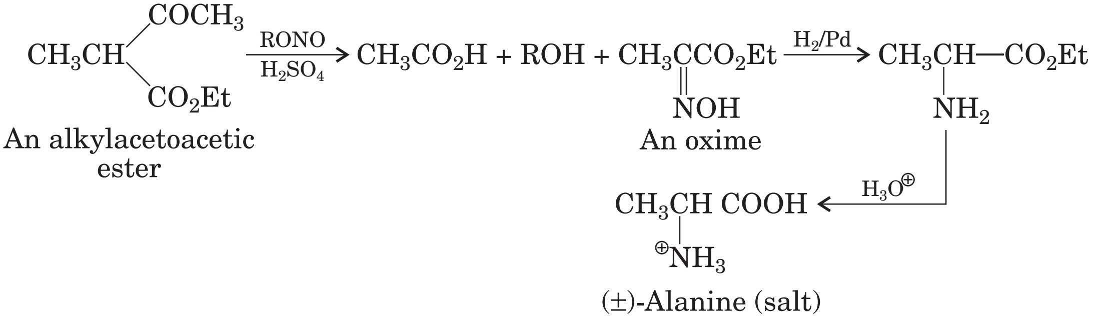


(b) **Darapsky Synthesis:** When an aldehyde is condensed with ethyl cyanoacetate and simultaneously hydrogenated in the presence of catalyst (reductive condensation), an alkyl cyanoacetic ester is obtained. Treatment of the resulting ester with hydrazine followed by nitrous acid affords the corresponding acyl azide. This, when subjected to Curtius reaction followed by hydrolysis produces an α-amino acid. Lucine, for example, can be prepared as follows:

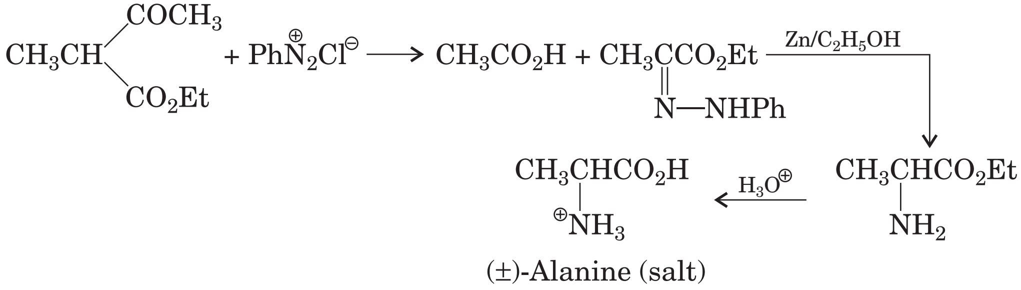


(viii) Reduction of oximes and hydrazones of α-keto acids

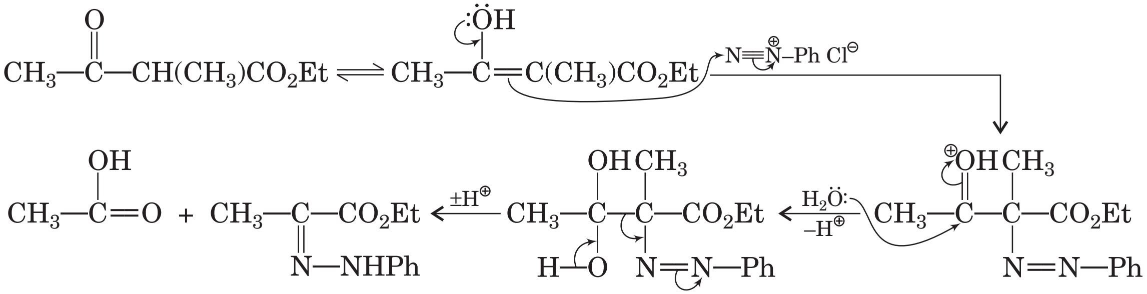
(a) Reduction of oximes When the oxime of an α-keto acid is reduced catalytically, an α-amino acid is obtained. This method is advantageous because the oximes may readily be prepared in good yield by allowing an alkylacetoacetic ester to react with an alkyl nitrite in the presence of sulphuric acid. Alanine, for example, can be prepared as follows:



(b) Reduction of hydrazones When an alkylacetoacetic ester is allowed to react with benzenediazonium chloride, a phenyl hydrazone is obtained. The hydrazone produces an α-amino ester when reduced with Zn/ethanol. The ester is finally hydrolyzed by dilute acid to yield an α-amino acid. Alanine, for example, can be prepared as follows:

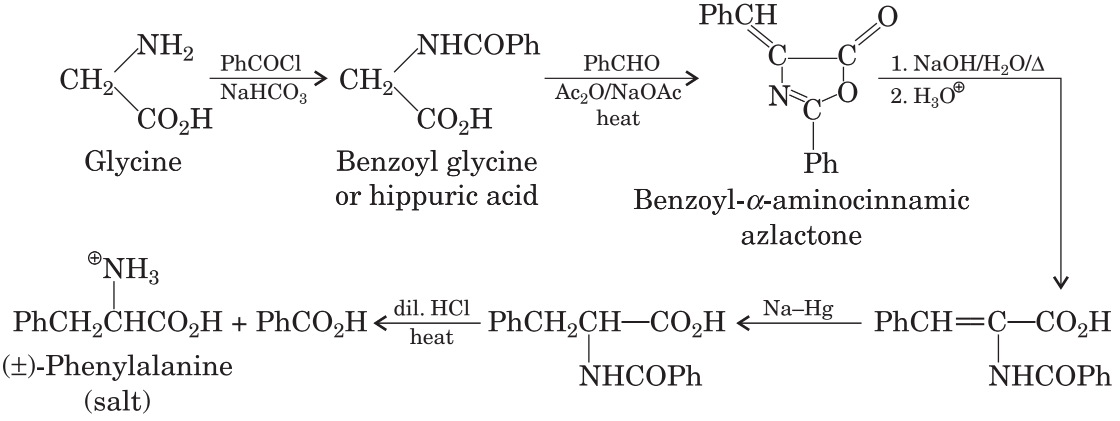


*** Mechanism:**

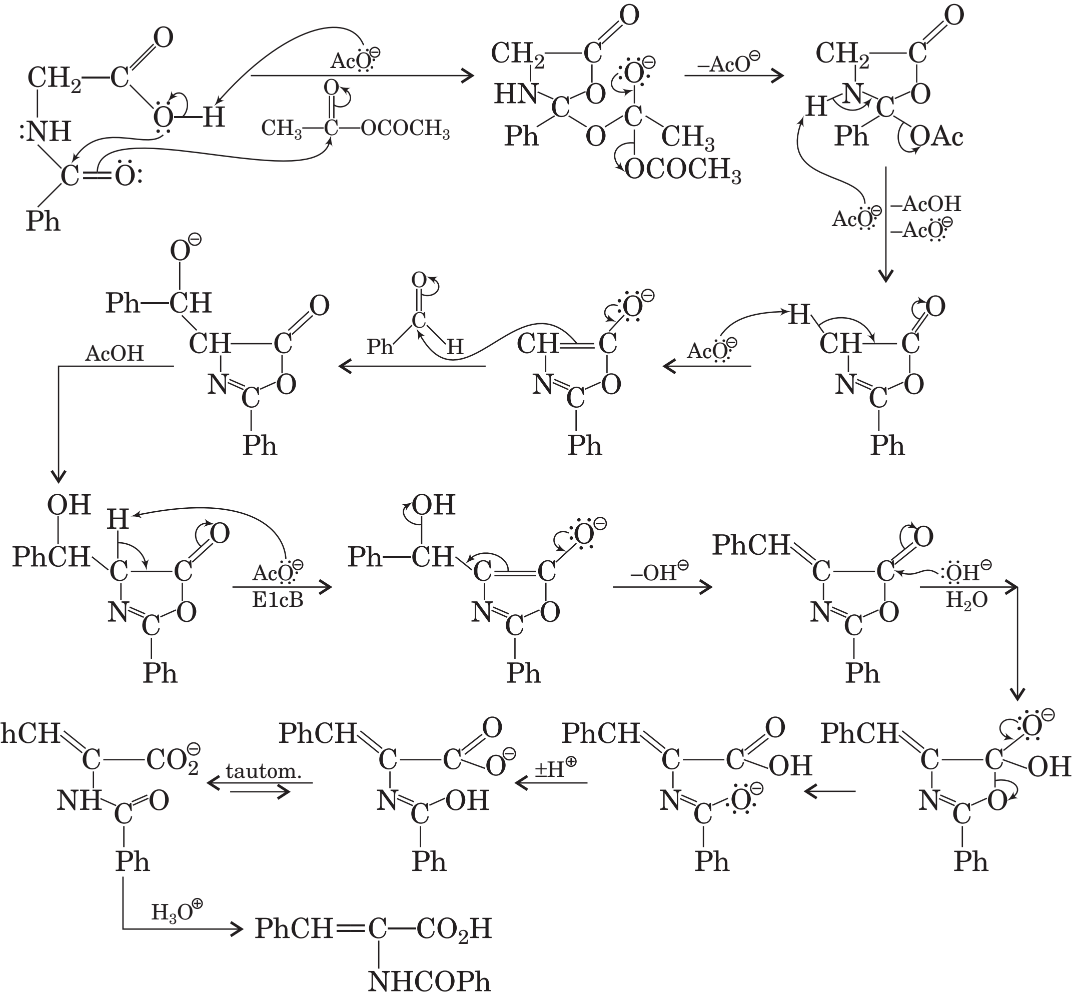


(ix) Through the formation of azlactone by Erlenmeyer synthesis

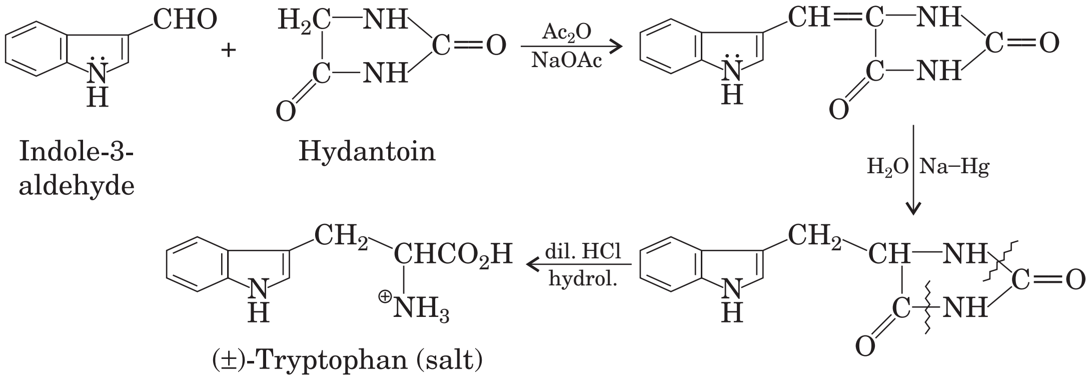
When an aromatic aldehyde is heated with benzoyl glycine (hippuric acid) in the presence of acetic anhydride and sodium acetate, an azalactone is obtained. This reaction is usually referred to as the *Erlenmeyer azlactone synthesis*. The azlactone ring opens up on warming with 1% NaOH solution. When the resulting α, β-unsaturated acid is reduced with sodium amalgam followed by hydrolysis with dilute acid, an α-amino acid is formed. Phenylalanine, for example, may be prepared conveniently by using this sequence of reactions:



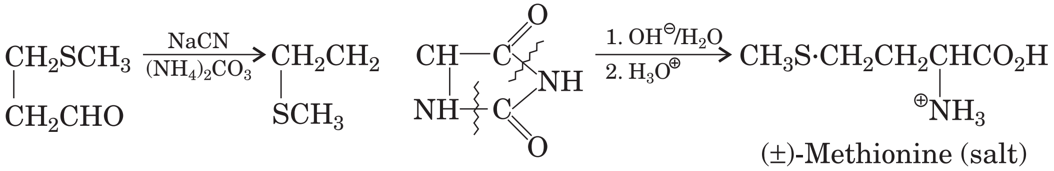
Mechanism A plausible mechanism for the formation and ring opening of azlactone may be sketched as follows:



(x) (a) Hydantoin synthesis Aromatic aldehydes condense with hydantoin in the presence of Ac_2O/NaOAc. When the product so obtained is reduced with sodium amalgam, followed by hydrolysis, an *α*-amino acid is obtained. Tryptophan, for example, may be prepared from indole-3-aldehyde (prepared from indole by means of the Reimer–Tiemann reaction) by this method.



(b) Bucherer hydantoin synthesis In this method, an aldehyde is first converted into a substituted hydantoin by treating it with ammonium carbonate and sodium cyanide in aqueous ethanol solution. When the resulting substituted hydantoin is subjected to alkaline hydrolysis followed by acidification, an α-amino acid is obtained. Methionine, for example, may be prepared by this method as follows:

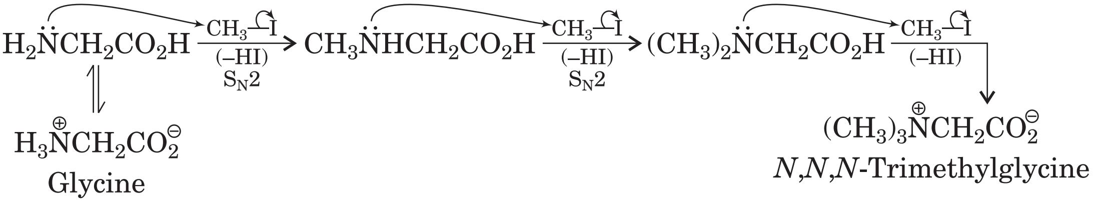


10.1.7 Reactions of Amino Acids

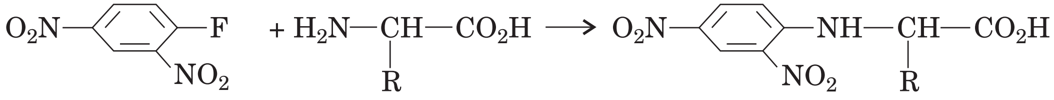
Amino acids undergo chemical reactions typical of both the carboxyl and amino groups. In addition, they undergo reactions involving both the functionalities. Some of their important reactions are given below:

(a) Reactions due to the amino (—NH$_2$) group

(i) Alkylation Amino acids undergo alkylation on treatment with alkyl halides. When a large excess of alkyl halide is used internal quaternary alkylammonium salts are formed. These salts having zwitterionic character are known as *betaines*. Treatment of glycine with an excess of methyl iodide, for instance, give rise to betaine (*N*,*N*,*N*-trimethylglycine), the simplest member of the series.



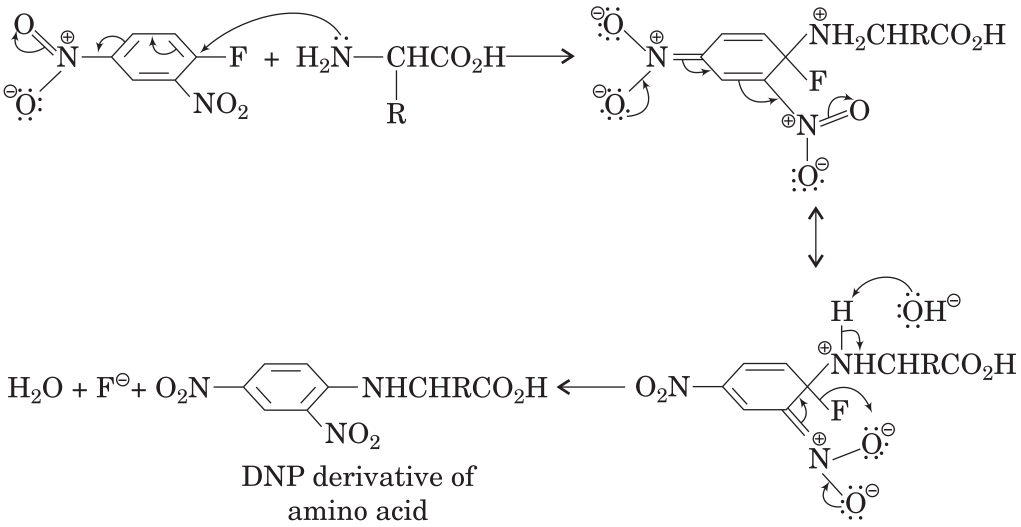
(ii) Arylation Amino acids react with 2,4-dinitrofluorobenzene (*Sanger's reagent*) in slightly alkaline solution to form a substituted dinitroaniline. These reactions proceed *via* nucleophilic aromatic substitution. A very useful application of this reagent will be discussed later.



Sanger's reagent

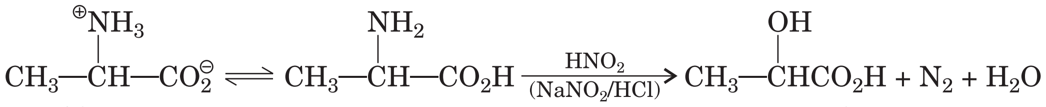
DNP derivative of an amino acid

Mechanism:



DNP derivative of amino acid

(iii) Action of nitrous acid When an amino acid is subjected to react with nitrous acid ($NaNO_2/HCl$), the amino group is converted to an —OH group, i.e., a hydroxy acid is obtained and nitrogen is evolved quantitatively. Alanine, for example produces lactic acid with HNO_2.

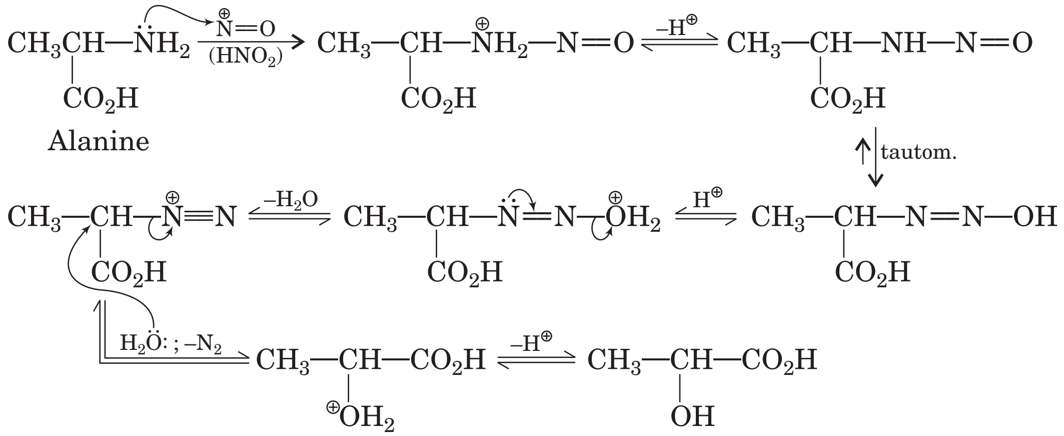


$$CH_3-\overset{\overset{\oplus}{N}H_3}{\overset{|}{C}H}-CO_2^{\ominus} \rightleftharpoons CH_3-\overset{NH_2}{\overset{|}{C}H}-CO_2H \xrightarrow[(NaNO_2/HCl)]{HNO_2} CH_3-\overset{OH}{\overset{|}{C}}HCO_2H + N_2 + H_2O$$

Alanine

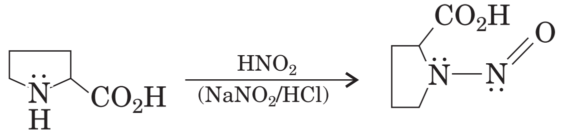
Lactic acid

Mechanism:



Alanine

Proline and hydroxyproline are 2° amines. So, they do not liberate N_2 upon treatment with nitrous acid. However, they react with nitrous acid to give the corresponding *N*-nitroso compounds.

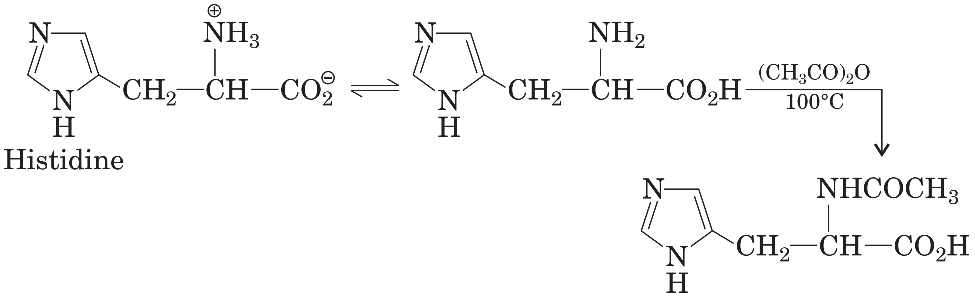


Proline

N-Nitrosoproline

(iv) Acylation Amino acids undergo acetylation and benzoylation when treated with acetyl chloride or acetic anhydride and benzoyl chloride, respectively. For example:

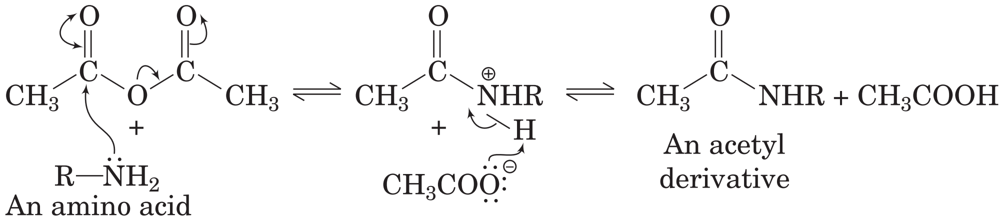
1.



Histidine

N-Acetylhistidine

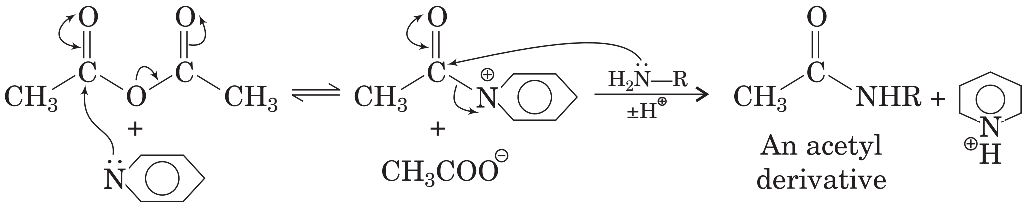
Mechanism:



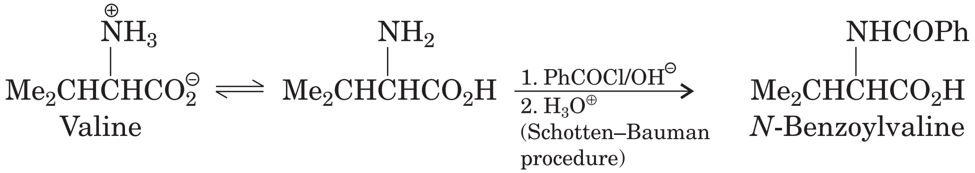
An amino acid

An acetyl derivative

In the presence of pyridine, acetylation of an amino acid occurs as follows:



2.



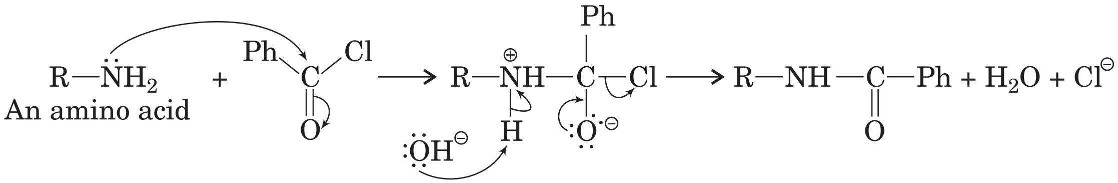
$$Me_2CH\underset{}{\overset{\overset{\oplus}{N}H_3}{C}}HCO_2^{\ominus} \rightleftharpoons Me_2CH\overset{NH_2}{C}HCO_2H \xrightarrow[\text{2. }H_3O^{\oplus}]{\text{1. PhCOCl/OH}^{\ominus}} Me_2CH\overset{NHCOPh}{C}HCO_2H$$

Valine

(Schotten–Bauman procedure)

N-Benzoylvaline

Mechanism:



(v) Reaction with formaldehyde When an amino acid is allowed to react with formaldehyde, a mixture of two products are obtained. Glycine, for example, reacts with one molar equivalent of HCHO, to yield methyleneglycine and with two molar equivalents of HCHO to yield dimethylolglycine.

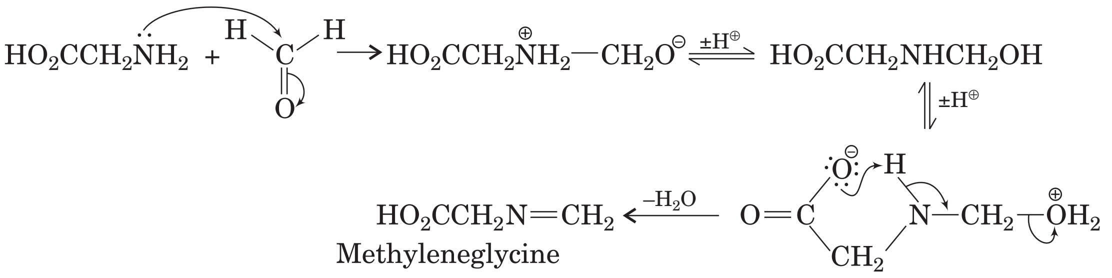
$$H_3\overset{\oplus}{N}CH_2CO_2^{\ominus} \rightleftharpoons H_2\ddot{N}CH_2CO_2H \xrightarrow{HCHO} CH_2{=}N{-}CH_2CO_2H + H_2O$$

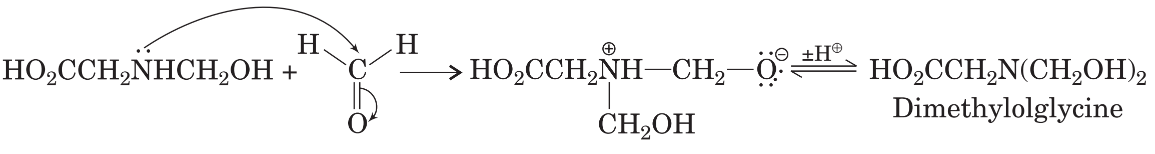
Methyleneglycine

or, $$H_3\overset{\oplus}{N}CH_2CO_2^{\ominus} \rightleftharpoons H_2\ddot{N}CH_2CO_2H \xrightarrow{2\ HCHO} (HOCH_2)_2CH_2CO_2H$$

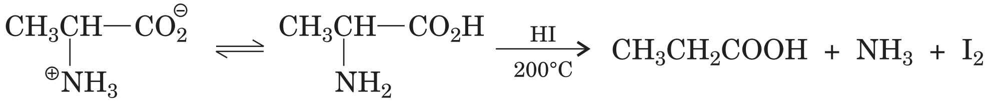
Dimethylolglycine

Mechanism:





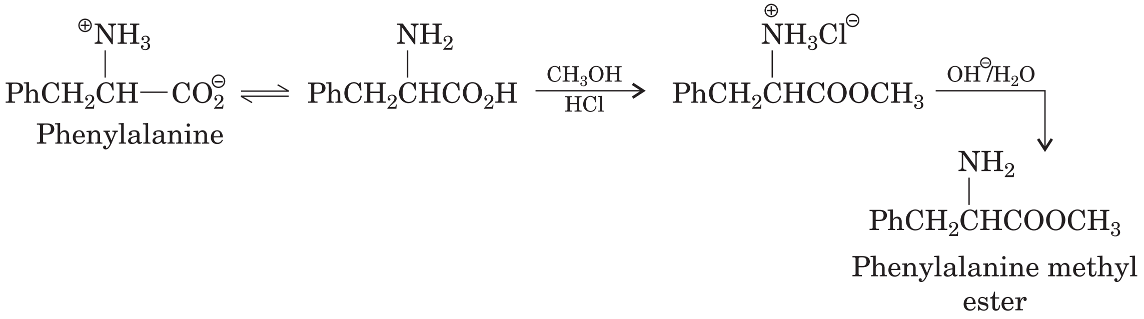
(vi) Action of hydroiodic acid When an amino acid is heated with hydroiodic acid (HI) at 200°C, the amino group of the amino acid is eliminated and as a result, a carboxylic acid is obtained. Alanine for example, reacts with HI at 200°C to yield propanoic acid.



$$CH_3\underset{\overset{\oplus}{N}H_3}{CH}-CO_2^{\ominus} \rightleftharpoons CH_3\underset{NH_2}{CH}-CO_2H \xrightarrow[200°C]{HI} CH_3CH_2COOH + NH_3 + I_2$$

(b) Reactions due to the carboxyl (—CO_2H) group:

(i) Esterification The carboxyl group of an amino acid can be esterified by treatment with an alcohol in the presence of dry HCl. The resulting amino ester hydrochloride gives the free amino acid on treatment with cold dilute alkali. Phenylalanine methyl ester, for example, may be obtained as follows:

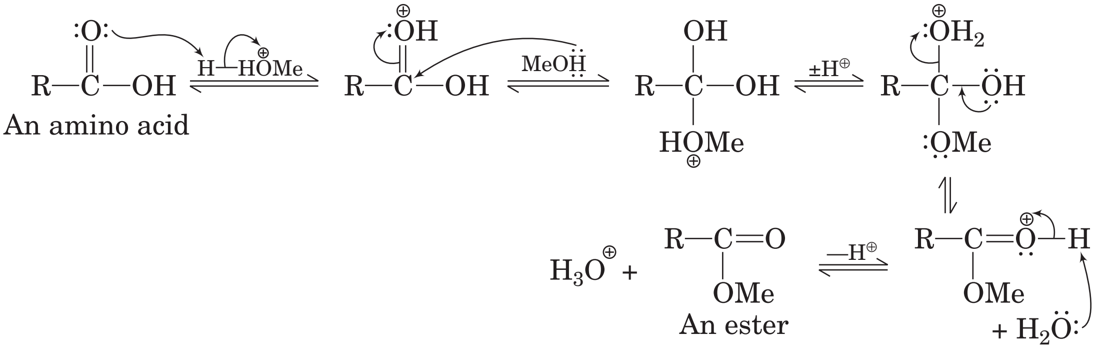


$$PhCH_2\overset{\overset{\oplus}{N}H_3}{CH}-CO_2^{\ominus} \rightleftharpoons PhCH_2\overset{NH_2}{C}HCO_2H \xrightarrow[HCl]{CH_3OH} PhCH_2\overset{\overset{\oplus}{N}H_3Cl^{\ominus}}{C}HCOOCH_3 \xrightarrow{OH^{\ominus}/H_2O} PhCH_2\overset{NH_2}{C}HCOOCH_3$$

Phenylalanine

Phenylalanine methyl ester

Mechanism:



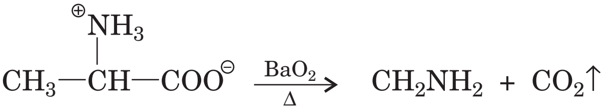
(ii) Formation of acid chlorides Conversion of amino acids into the corresponding acid chlorides is quite a difficult process since direct treatment of amino acids with phosphorus pentachloride, thionyl chloride, *etc.*, fails to give the chloride because of the presence of —NH_2 group. This can, however, be achieved by allowing the acyl derivative of an amino acid with $SOCl_2$.

$$RCONHCH_2COOH + SOCl_2 \longrightarrow RCONHCH_2COCl + HCl\uparrow + SO_2\uparrow$$

An acyl derivative of an amino acid

An acid chloride

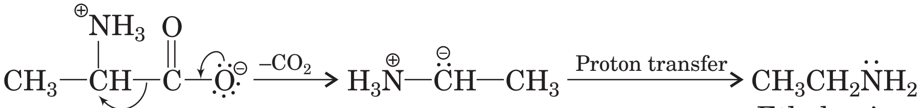
(iii) Decarboxylation When amino acids are heated in the presence of BaO_2, they undergo decarboxylation yielding the corresponding amines. For example:



$$CH_3-\overset{\overset{\oplus}{N}H_3}{\overset{|}{C}H}-COO^{\ominus} \xrightarrow[\Delta]{BaO_2} CH_2NH_2 + CO_2\uparrow$$

Alanine Ethylamine

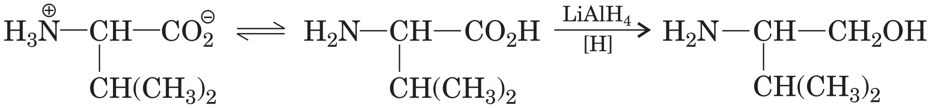
Mechanism:



$$CH_3-\overset{\overset{\oplus}{N}H_3}{\overset{|}{C}H}-\overset{\overset{O}{\|}}{C}-\ddot{\underset{..}{O}}:^{\ominus} \xrightarrow{-CO_2} H_3\overset{\oplus}{N}-\overset{\ominus}{\ddot{C}}H-CH_3 \xrightarrow{\text{Proton transfer}} CH_3CH_2\ddot{N}H_2$$

Ethylamine

(iv) Reduction When amino acids are reduced with lithium aluminium hydride, they are converted into the corresponding alcohols without any loss of optical activity.

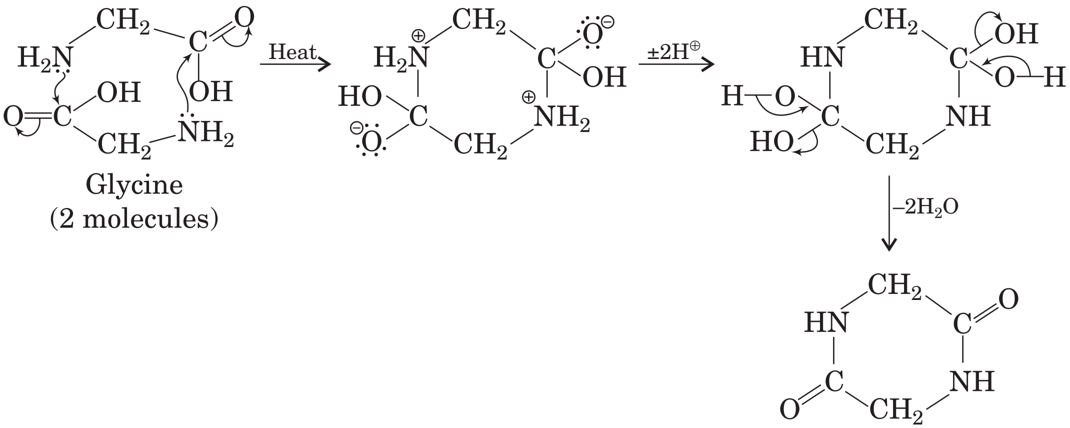


$$H_3\overset{\oplus}{N}-\underset{\underset{CH(CH_3)_2}{|}}{CH}-CO_2^{\ominus} \rightleftharpoons H_2N-\underset{\underset{CH(CH_3)_2}{|}}{CH}-CO_2H \xrightarrow[\text{[H]}]{LiAlH_4} H_2N-\underset{\underset{CH(CH_3)_2}{|}}{CH}-CH_2OH$$

Valine 2-Amino-3-methyl-1-butanol

(c) Reactions due to both amino and carboxyl groups:

(i) Effect of heat (dehydration) When an α-amino acid is heated two molecules of it react in such a way that the $—NH_2$ group of one forms amide with the $—CO_2H$ group of the other. A cyclic diamide is obtained as a result of intermolecular dehydration. Glycine, for example, produces 2,5-diketopiperazine.

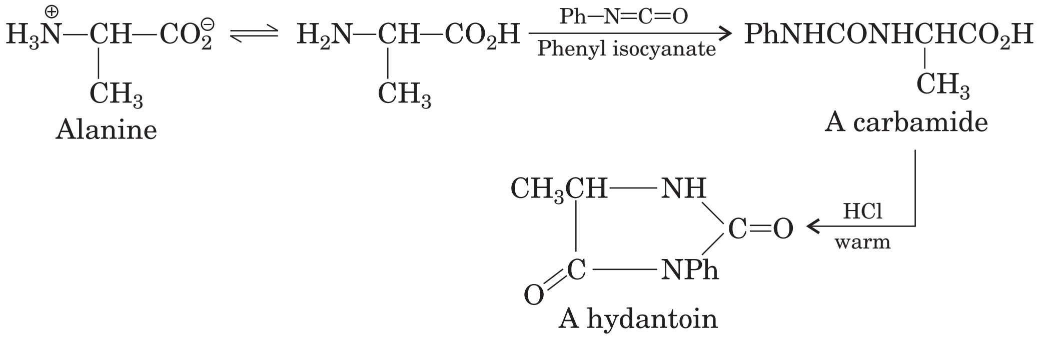


Glycine
(2 molecules)

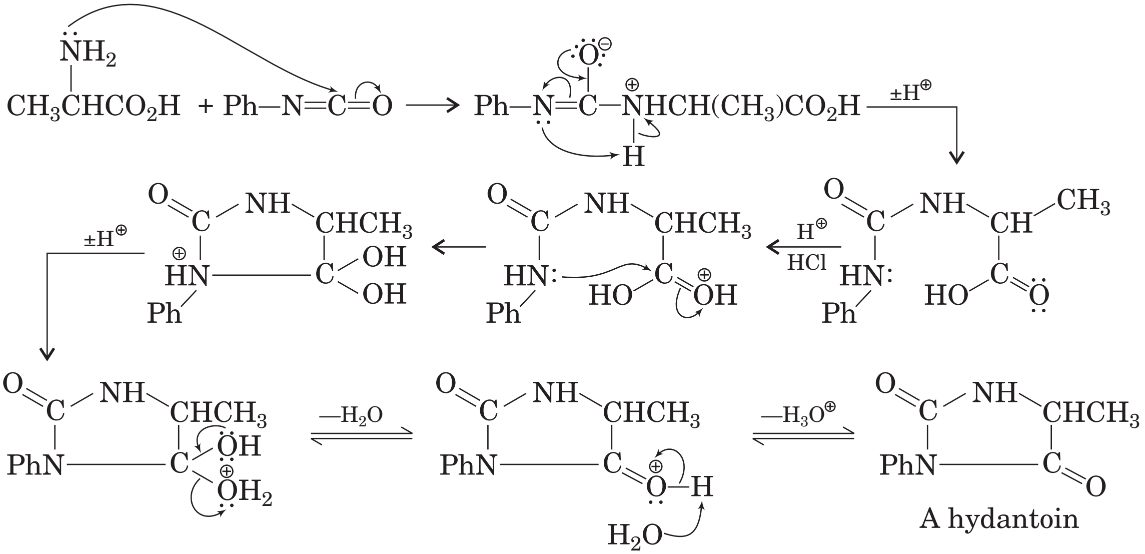
2,5-Diketopiperazine
(a cyclic diamide)

It is to be noted that β-amino acids suffer β-elimination of NH_3 forming α,β-unsaturated acids, while γ- and δ-amino acids undergo intramolecular dehydration yielding *lactams*.

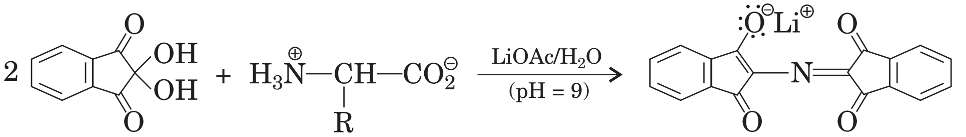
(ii) Formation of hydantoin Amino acids reacts with isocyanates to form the corresponding carbamides which on warming with hydrochloric acid produce hydantoins. For example:



Mechanism:



(iii) Ninhydrin reaction When ninhydrine (indane–1,2,3-trione hydrate) is allowed to react with an aqueous solution of an amino acid in the presence of LiOAc (pH = 9), an intensely coloured purple anion (called *Ruhemann's purple*) is obtained. The formation of this purple colour is used to detect amino acids. All amino acids (except proline and hydroxyproline which give a yellow colour) regardless of the identity of the R groups, form the same purple compound when react with ninhydrin and this is because in this reaction the R-group of the amino acid is lost as an aldehyde, i.e., as RCHO. The reaction may be represented as follows:



Ninhydrin An amino acid Ruhemann's purple

+ RCHO + CO_2 + AcOH + $2H_2O$

An aldehyde

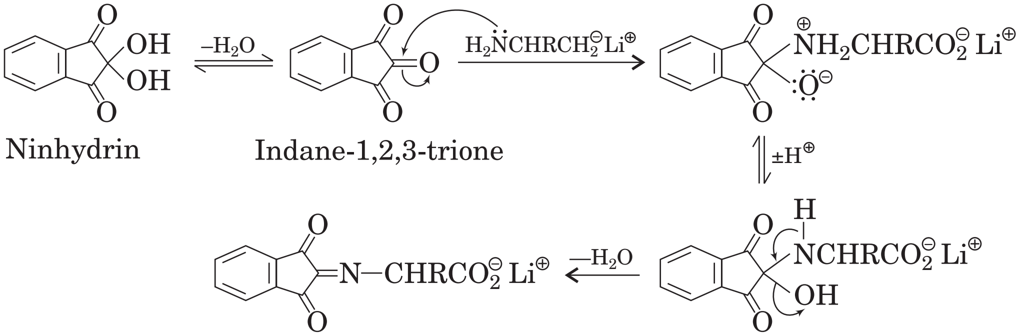
Mechanism:

The mechanism of the reaction involves the steps as follows:

Step 1: Formation of an imine (a Schiff's base)

$$Li^{\oplus}OAc^{\ominus} + H_2O \rightleftharpoons (Li^{\oplus} + OH^{\ominus}) + AcOH$$

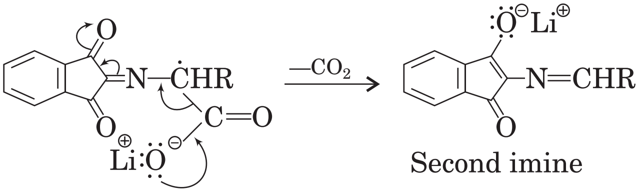
$$H_3\overset{\oplus}{N}—CHR—CO_2^{\ominus} + LiOH \rightleftharpoons H_2N—CHR—CO_2^{\ominus}Li^{\oplus} + H_2O$$



Ninhydrin Indane-1,2,3-trione

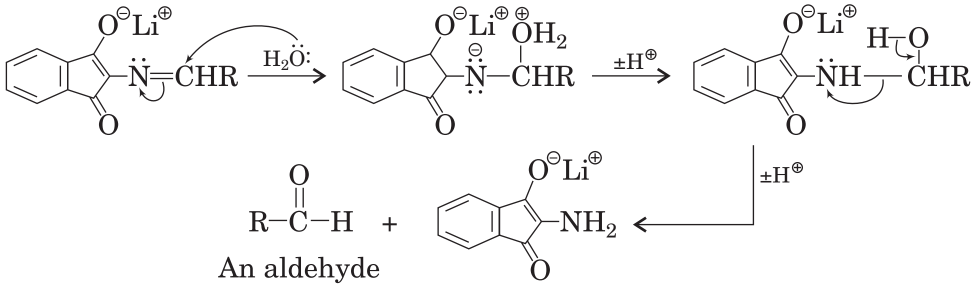
First imine

Step 2: Decarboxylation of the first imine to yield a second imine (a Schiff's base)



Second imine

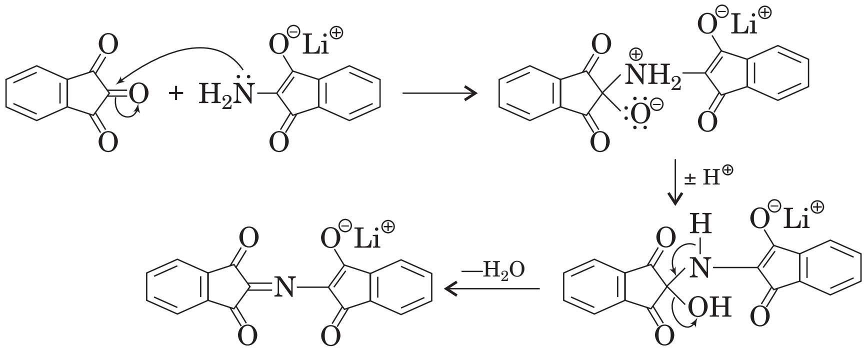
Step 3: Hydrolysis of the second imine to form an amine



An aldehyde

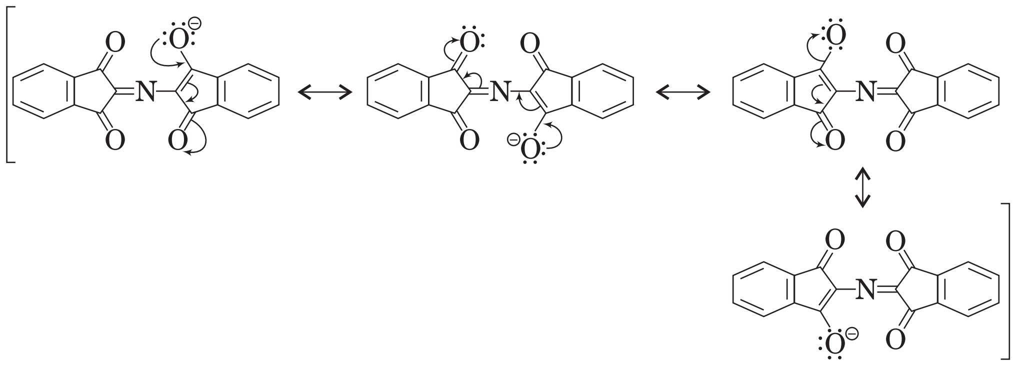
An amine

Step 4: Condensation of a second molecule of indane-1,2,3-trione with the resulting amine to form the purple coloured compound



Ruhemann's purple
(a purple anion)

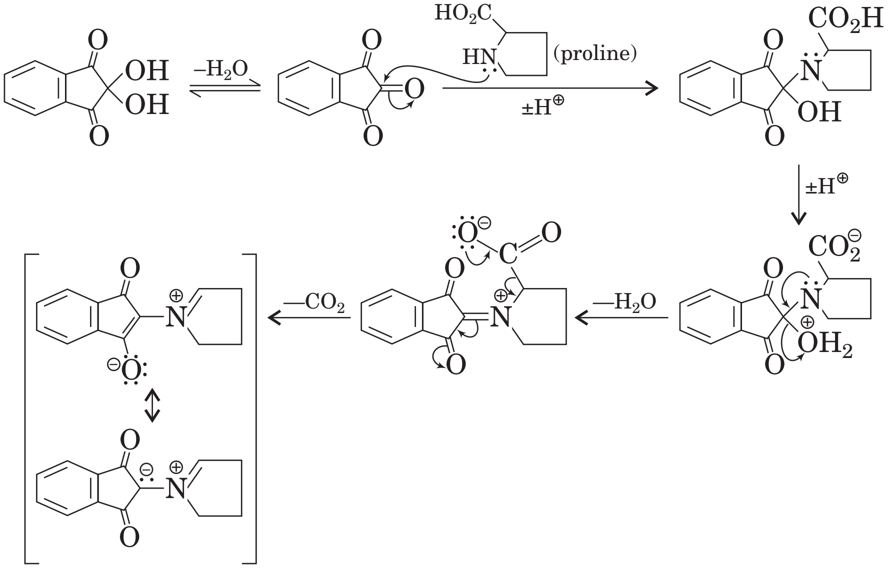
The purple compound is highly stabilized by resonance involving four equivalent resonance structures.



Because of extensive electron delocalization leading to very low energy absorption in the visible region (colour absorbed: green; wavelength absorbed : 500–560 nm), the compound exhibits purple colour.

It is to be noted that the only portion of the purple compound derived from the amino acid is the nitrogen.

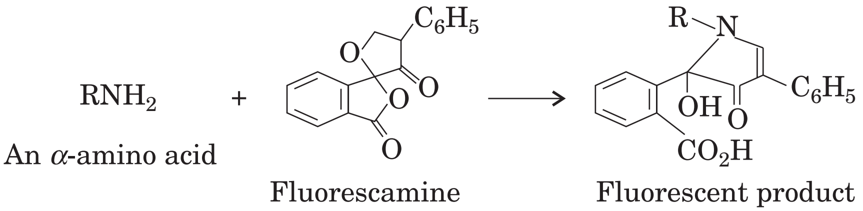
Behaviour of proline and hydroxyproline The two amino acids do not react with ninhydrin like other amino acids and this is because their *α*-amino groups are part of a five-membered ring (secondary amines). They give different compound when react with ninhydrin. These absorb light at different wavelengths and therefore, they exhibit yellow colour instead of purple. When proline is allowed to react with ninhydrin, the following yellow compound with a structure probably stabilized by the contribution of an ylide form is obtained.



An ylide
(yellow)

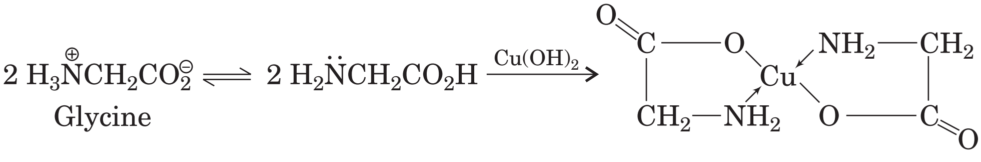
Ninhydrin is a reagent which is also widely used for the quantitative measurement of amino acids. After separation by some chromatographic methods, the amino acids are treated with ninhydrin reagent and the concentration of the purple colour developed is measured spectrophotometrically.

A new very sensitive method of detection and analysis of amino acids, which is useful down to the 10^{-12} mole level depends on the formation from RNH_2 and fluorescamine, of substances which are intensively fluorescent in UV light.



Proline and hydroxyproline are exceptions because neither has the necessary primary —NH_2 group needed for the reaction.

(iv) Formation of metal chelates A few amino acids form complex salts when reacts with solutions of metal oxides or hydroxides. Glycine, for example, reacts with cupric hydroxide to form deep-blue needles of a copper salt.

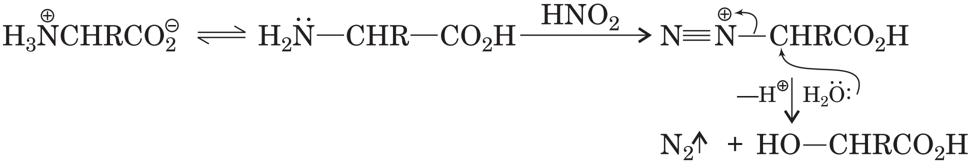


Copper glycinate
(deep blue needles)

10.1.8 Estimation of α-Amino Acids

There are several methods by which α-amino acids can be estimated. Two important methods are discussed below:

(a) van Slyke method This method is based upon the measurement of the volume of nitrogen gas liberated when an amino acid is treated with nitrous acid.



During the experiment, some unstable HNO_2 decomposes to give nitric oxide (NO).

$$3HNO_2 \longrightarrow HNO_3 + H_2O + 2NO\uparrow$$

Therefore, a mixture of N_2 and NO is obtained. The mixture is then passed through alkaline $KMnO_4$ solution whereupon the nitric oxide is absorbed. The residual nitrogen is measured. One molar volume of nitrogen at STP is equivalent to one —NH_2 group.

(b) Sorensen formal titration Amino acids are present in aqueous solution largely as zwitterions and cannot be titrated directly with standard alkali owing to the buffering effect of the zwitterions. If the aqueous solution of an amino acid is treated with an excess of a carefully neutralized solution of HCHO, it can then be titrated with a solution of a strong alkali. Formaldehyde reacts with the amino group of amino acids to give condensation and addition products. For example:

$$\underset{\text{Glycine}}{H_3\overset{\oplus}{N}CH_2CO_2^{\ominus}} \rightleftharpoons H_2NCH_2CO_2H \xrightarrow{HCHO} \underset{\text{Methyleneglycine}}{CH_2{=}NCH_2CO_2H} + H_2O$$

or,

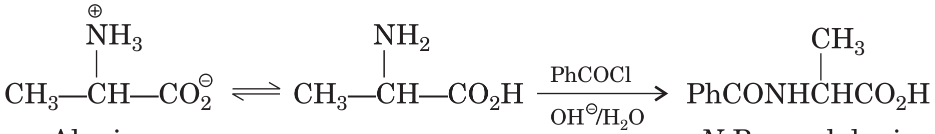
$$\underset{\text{Glycine}}{H_3\overset{\oplus}{N}CH_2CO_2^{\ominus}} \rightleftharpoons H_2NCH_2CO_2H \xrightarrow{2HCHO} \underset{\text{Dimethylolglycine}}{(CH_2OH)_2NCH_2CO_2H}$$

This treatment 'masks' the amino group and hence the carboxyl group can be easily titrated with alkali. This method of estimating amino acids is known as *Sorensen formal titration*.

10.1.9 Resolution of DL-Amino Acids

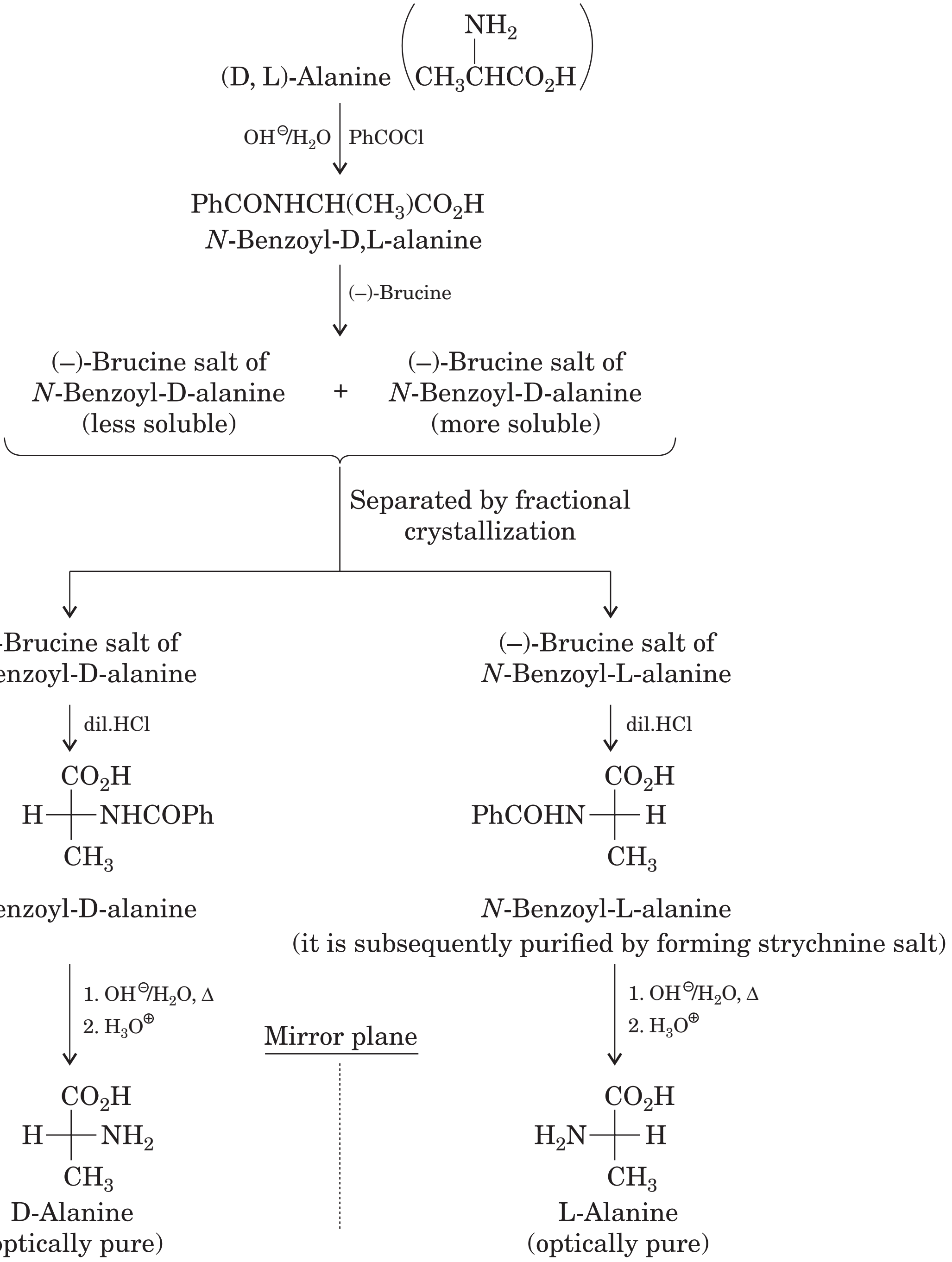
When α-amino acids are synthesized in nature, only the L-enantiomer is produced. However, with the exception of glycine which has no chirality centre, all the laboratory syntheses of amino acids produce racemic products. Pure L-enantiomers (biologically active) are required for peptide synthesis. Therefore, to obtain the naturally occurring L-amino acid, we must, of course, resolve the racemic form. The two important methods for resolving amino acids into their enantiomers are as follows:

(a) The diastereoisomeric salt method Since neutral amino acids remain in zwitterionic form, it is not possible to resolve them either as an acid or as a base. They need to be converted into such derivatives which can subsequently be resolved either as an acid or a base. The amino acid is usually converted into an amide. The resulting amide, which is a typical acid, is then allowed to react with one enantiomer of a chiral base. Two diastereoisomeric salts are obtained. They are separated by fractional crystallization by taking advantage of their different solubilities. Removal of the chiral base followed by hydrolysis of the amide results in formation of pure enantiomeric amino acids. Alanine, for example, may be resolved as follows. It is first treated with benzoyl chloride in the presence of aqueous base to yield *N*-benzoylalanine, which is a typical acid.



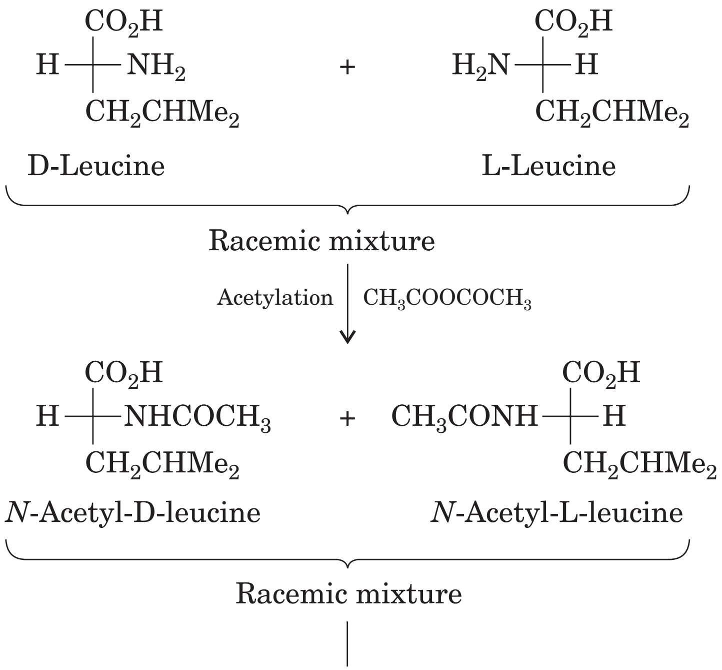
$$\underset{\text{Alanine}}{CH_3{-}\overset{\overset{\oplus}{N}H_3}{\overset{|}{C}H}{-}CO_2^{\ominus}} \rightleftharpoons CH_3{-}\overset{NH_2}{\overset{|}{C}H}{-}CO_2H \xrightarrow[OH^{\ominus}/H_2O]{PhCOCl} \underset{N\text{-Benzoylalanine}}{PhCONH\overset{CH_3}{\overset{|}{C}}HCO_2H}$$

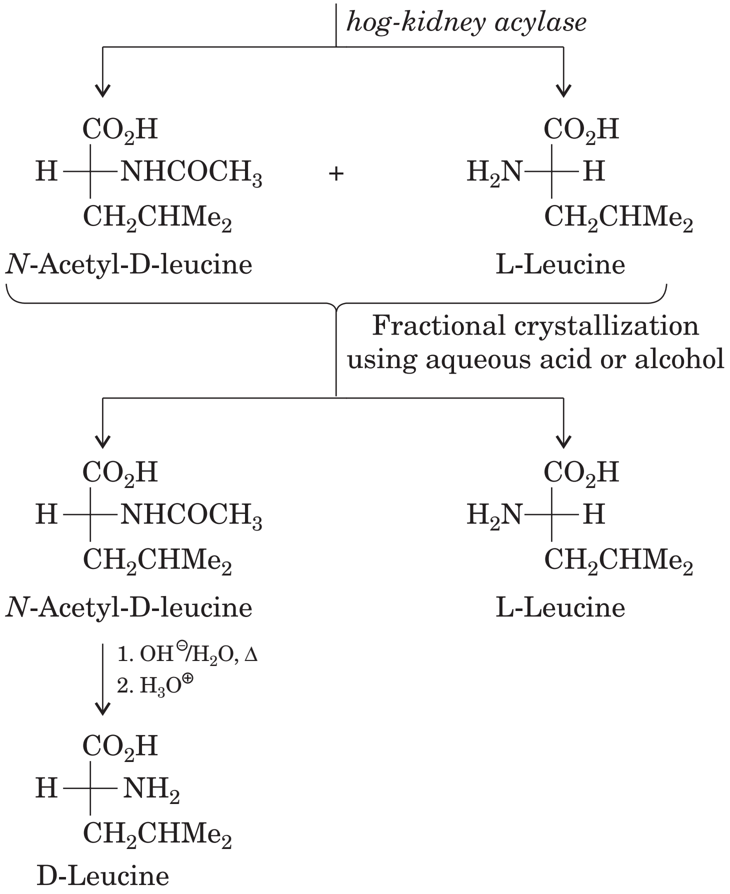
Racemic *N*-benzoylalanine is then resolved in the normal way with the optically active base brucine or strychnine as follows:


(D, L)-Alanine $\left(CH_3\overset{NH_2}{C}HCO_2H\right)$
$OH^{\ominus}/H_2O$ PhCOCl
$PhCONHCH(CH_3)CO_2H$
N-Benzoyl-D,L-alanine
(–)-Brucine
(–)-Brucine salt of N-Benzoyl-D-alanine (less soluble)
+
(–)-Brucine salt of N-Benzoyl-D-alanine (more soluble)
Separated by fractional crystallization
(–)-Brucine salt of N-Benzoyl-D-alanine
(–)-Brucine salt of N-Benzoyl-L-alanine
dil.HCl
dil.HCl
CO_2H H NHCOPh CH_3
CO_2H PhCOHN H CH_3
N-Benzoyl-D-alanine
N-Benzoyl-L-alanine (it is subsequently purified by forming strychnine salt)
1. $OH^{\ominus}/H_2O$, Δ
2. $H_3O^{\oplus}$
Mirror plane
1. $OH^{\ominus}/H_2O$, Δ
2. $H_3O^{\oplus}$
CO_2H H NH_2 CH_3
D-Alanine (optically pure)
CO_2H H_2N H CH_3
L-Alanine (optically pure)

The enantiomer which forms the less soluble salt is usually obtained in an optically pure state. Since the brucine salt of *N*-benzoyl-D-alanine is less soluble, it is obtained in an optically pure state and as a consequence, D-alanine is obtained in an optically pure state. The brucine salt of *N*-benzoyl-L-alanine is usually isolated by evaporation of the solution. It must be optically impure because some of the less soluble salt invariably remains in solution. L-alanine is, therefore, isolated in optically impure state. The strychnine salt of *N*-benzoyl-L-alanine is less soluble and because of this, the impure *N*-benzoyl-L-alanine is treated with strychnine to give a crystalline and optically pure strychenine salt. In this way, both enantiomers of alanine are obtained in optically pure form.

(b) Enzymetic resolution Certain enzymes (biological catalysts) can be used to resolve racemic amino acids into enantiomers. Enzymes are chiral molecules and so, they react differently with the enantiomers of an amino acid. It has been observed that may enzymes catalyze the reaction of only one enantiomer. Therefore, when a racemic mixture is exposed to an enzyme, one enantiomer will react while the other remains unchanged and can be recovered. When an acylated amino acid is treated with enzyme *hog-kidney acylase*, the enzyme catalyzes the hydrolysis of *N*-acetyl-L-amino acid but does not catalyze the hydrolysis of *N*-acetyl-D-amino acid. The resulting mixture of acylated D-amino acid and deacylated L-amino acid is easily separated because the former is soluble only in base, while the latter is soluble in both acid and base. Finally, the D-amino acid is obtained when *N*-acetyl-D-amino acid is hydrolyzed with dilute acid. The resolution of (D,L)-leucine, for example, by using the enzyme *acylase* from *hog kidney* may be outlined as follows:



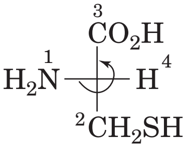


Because the resolution, i.e., separation of the enantiomers depends on the difference in the rate of reaction of the enzyme with the two *N*-acetylated compounds, this technique is known as a *kinetic resolution*. *D-Amino acid oxidase* may also be used to separate a racemic mixture of an amino acid.

SOLVED PROBLEMS

1. Explain why L-cysteine is unique in having *R* configuration, even though most naturally occurring amino acids have *S* configuration.

Solution In most naturally occurring L-amino acids, the —COOH group gets priority over the —R group and because of this, they have *S* configuration. However, in L-cysteine, the R- group, i.e., the —CH_2SH group gets priority over the —COOH group (because S has greater atomic number than O) and so, it is unique is having the *R* configuration.



L-Cysteine
(*R*)-Cysteine

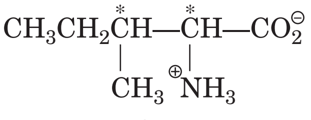
[Since 1 → 2 → 3 traces an anticlockwise path and the lowest priority ligand (H) is on the horizontal bond, the configuration is *R*.]

2. **What do you mean by complete and incomplete proteins?**

Solution Complete proteins are those which provide all the amino acids in about the right proportions for human nutrition, whereas incomplete proteins are those which are severely deficient in one or more of the essential amino acids.

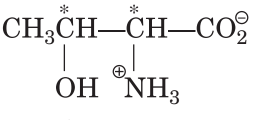
3. **Give the amino acids with more than one dissimilar chiral centres. Give Fischer projections for all the stereoisomers of one of them. Write their names with D/L and R/S designations.**

Solution There are three amino acids with more than one dissimilar chiral centres and these are as follows:



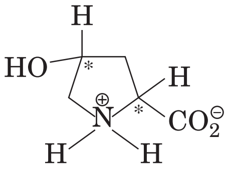
$$CH_3CH_2\underset{CH_3}{\underset{|}{\overset{*}{C}H}}—\underset{\overset{\oplus}{N}H_3}{\underset{|}{\overset{*}{C}H}}—CO_2^{\ominus}$$

Isoleucine

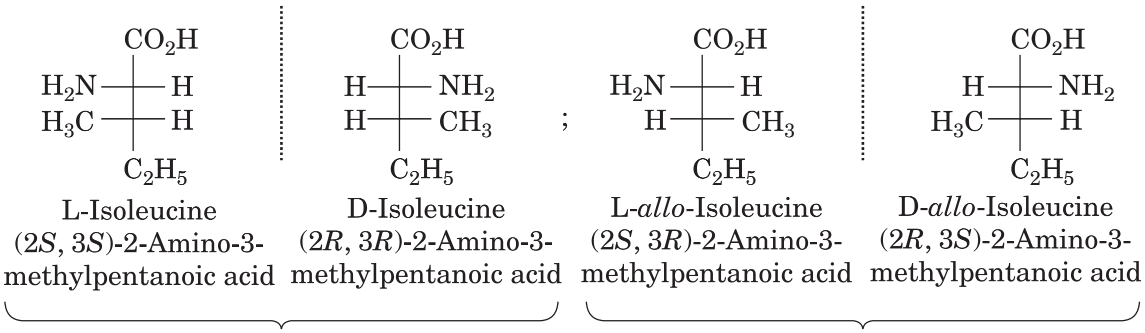


$$CH_3\underset{OH}{\underset{|}{\overset{*}{C}H}}—\underset{\overset{\oplus}{N}H_3}{\underset{|}{\overset{*}{C}H}}—CO_2^{\ominus}$$

Threonine



4-Hydroxyproline



L-Isoleucine
(2*S*, 3*S*)-2-Amino-3-methylpentanoic acid

D-Isoleucine
(2*R*, 3*R*)-2-Amino-3-methylpentanoic acid

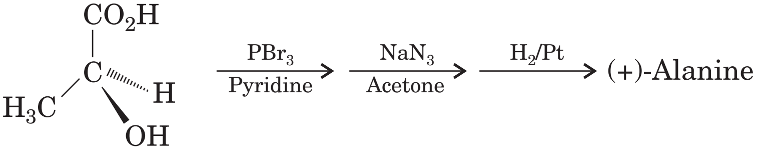
L-*allo*-Isoleucine
(2*S*, 3*R*)-2-Amino-3-methylpentanoic acid

D-*allo*-Isoleucine
(2*R*, 3*S*)-2-Amino-3-methylpentanoic acid

Enantiomers

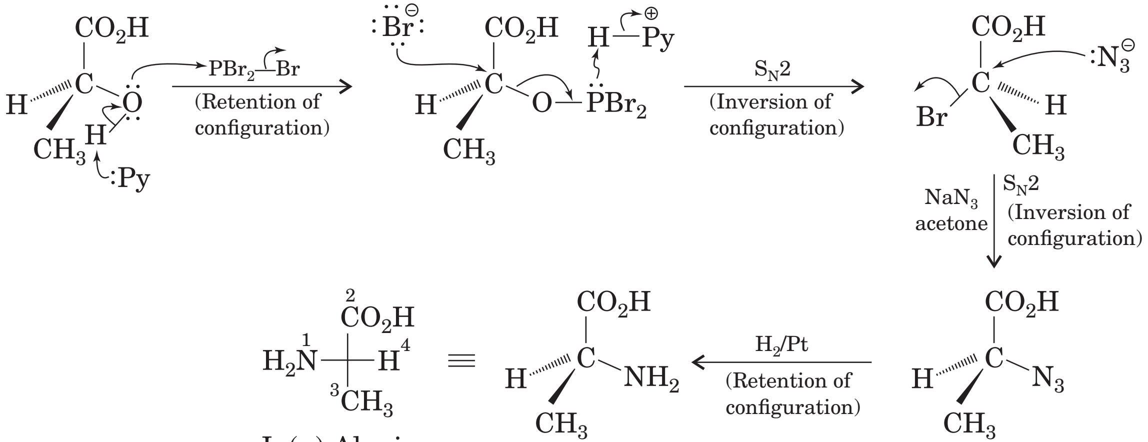
Enantiomers

4. **Predict the configuration of (+)-alanine which is related to L-(+)-lactic acid by the following sequence of reactions:**



L-(+)-Lactic acid

Solution


CO_2H
PBr₂—Br
(Retention of configuration)
:Py
S_N2
(Inversion of configuration)
$N_3^\ominus$
NaN₃ acetone
S_N2
(Inversion of configuration)
H₂/Pt
(Retention of configuration)
NH₂
N₃
≡

L-(+)-Alanine
or, (*S*)-Alanine

Hence, (+)-alanine has *S* configuration.

5. Explain the following observations:

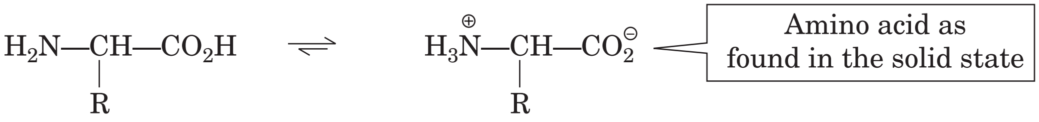
(a) Amino acids are nonvolatile crystalline solids and most of them decompose rather than melt at fairly high temperatures.

(b) Amino acids are appreciably soluble in water but insoluble in nonpolar solvents.

(c) Amino acids have much larger dipole moments (μ) than simple amines or simple acids.

(d) Amino acids are less acidic than most carboxylic acids and less basic than most amines.

Solution Although we commonly write amino acids with an intact carboxyl (—COOH) group and amino (—NH_2) group, their actual structure is ionic and this is because the carboxyl group loses a proton to form a carboxylate ion, and the amino group accepts that proton to form an ammonium ion.



$$\underset{\text{Uncharged structure (minor)}}{H_2N\text{—}\underset{\displaystyle R}{\underset{|}{CH}}\text{—}CO_2H} \rightleftharpoons \underset{\text{Dipolar ion or zwitterion (major)}}{H_3\overset{\oplus}{N}\text{—}\underset{\displaystyle R}{\underset{|}{CH}}\text{—}CO_2^{\ominus}}$$

Amino acid as found in the solid state

Uncharged structure (minor)

Dipolar ion or zwitterion (major)

(a) That amino acids are crystalline solids is a consequence of the strong intermolecular electrostatic forces of attraction. These attractions stabilize the solid state and resist conversion of the solid state into a liquid. Because of this salt-like nature, amino acids decompose rather than melt at high temperatures.

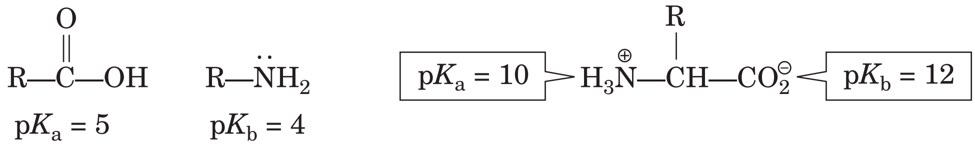
(b) Since water solvates the ionic groups of amino acids by forming H-bonds and ion-dipole bonds. They are soluble in water. However, they are insoluble in nonpolar solvents like benzene, ether, etc. because these solvents are unable to solvate the ionic groups in the dipolar ion.

(c) Molecules containing a great deal of separated charge are expected to possess large dipole moment. Consequently, amino acids containing a great deal of separated charge possess a large dipole moment than simple amines or simple acids (in which there is no possibility of formation of zwitterion by proton transfer). For example:

$$H_3\overset{\oplus}{N}\text{—}CH_2\text{—}CO_2^{\ominus} \quad ; \quad CH_3CH_2CH_2NH_2 \quad ; \quad CH_3CH_2CO_2H$$

Glycine, $\mu = 14D$ Propylamine, $\mu = 1.4D$ Propanoic acid, $\mu = 1.7D$

(d) Amino acids are less acidic than most carboxylic acids and less basic than most amine because the acidic part of the amino acid molecule is the $\text{—}\overset{\oplus}{N}H_3$ group, not a —COOH group and the basic part is the $\text{—}COO^{\ominus}$ group and not a free $\text{—}\ddot{N}H_2$ group.

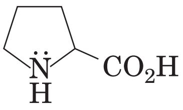


$$R\text{—}\overset{\overset{O}{\|}}{C}\text{—}OH \qquad R\text{—}\ddot{N}H_2 \qquad \boxed{pK_a = 10} \succ H_3\overset{\oplus}{N}\text{—}\overset{\overset{R}{|}}{C}H\text{—}CO_2^{\ominus} \prec \boxed{pK_b = 12}$$

$pK_a = 5$ $pK_b = 4$

6. Mention the structural feature that distinguishes proline from the other amino acids.

Solution Proline is a 2° amine and also, the amino N is part of a five-membered ring.



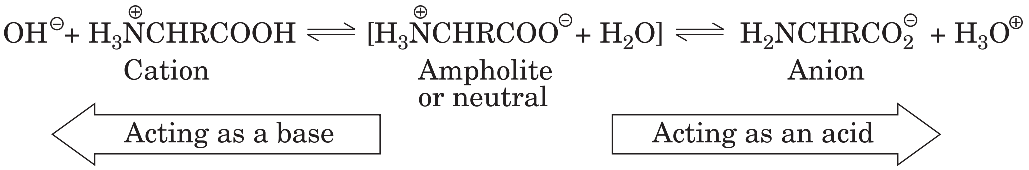
Proline

7. What are the D/L and *R*/*S* configurations of most naturally occurring amino acids?

Solution Configurations of most naturally occurring amino acids are L and *S*.

8. Explain why amino acids are amphoteric. Write equilibrium equations to show the atmospheric behaviour of an amino acid in aqueous medium. Mention the net charge of amino acid at p*I*, lower pH and higher pH.

Solution Because amino acids contain both acidic $(-\overset{\oplus}{N}H_3)$ and basic $(-CO_2^{\ominus})$ groups, they are amphoteric (having both acidic and basic properties).



$$OH^{\ominus} + H_3\overset{\oplus}{N}CHRCOOH \rightleftharpoons [H_3\overset{\oplus}{N}CHRCOO^{\ominus} + H_2O] \rightleftharpoons H_2NCHRCO_2^{\ominus} + H_3O^{\oplus}$$

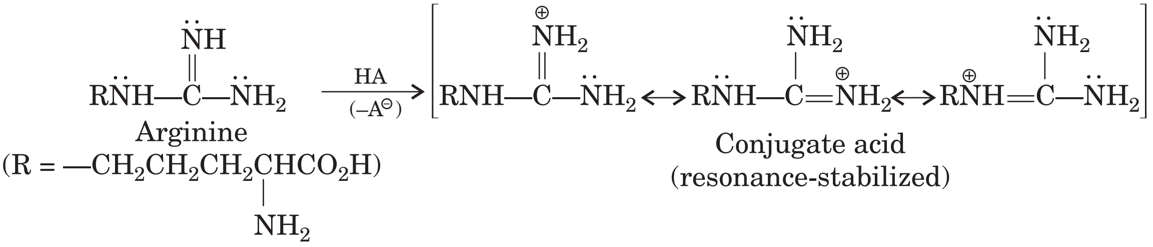
At the isoelectric point (p*I*), an amino acid has a net charge of zero, with $-\overset{\oplus}{N}H_3$ and $-COO^{\ominus}$ balancing each other. In more acidic solution (lower pH), the $-COO^{\ominus}$ group becomes protonated and the net charge is positive. In more basic solution (higher pH), the $-\overset{\oplus}{N}H_3$ group loses its proton and the net charge is negative.

9. Explain why amino acids are least soluble at p*I* but most soluble at pH < 2 or pH > 11.

Solution At the isoelectric pH or isoelectric point (p*I*), the concentrations of the cationic and anionic forms are equal but least, and that of the dipolar ion or zwitterion is the highest. However, because of intermolecular electrostatic and H-bonding interactions, the dipolar ion does not get hydrated appreciably and thus an amino acid has least solubility in water at p*I*. On the other hand, the cationic ($H_3\overset{\oplus}{N}CHRCO_2H$) and the anionic ($H_2NCHRCO_2^{\ominus}$) forms of amino acids get maximum hydrated and become most soluble in water. Since the concentrations of the cationic and the anionic forms are maximum at pH < 2 and pH > 11, respectively, amino acids are most soluble at pH < 2 (i.e., at strongly acidic solution) and at pH > 11 (i.e., at strongly alkaline solution).

10. The guanidine group ($\text{—}\ddot{N}H\text{—}\overset{\overset{\ddot{N}H}{\|}}{C}\text{—}\ddot{N}H_2$) of arginine is one of the most strongly basic of all organic groups. Explain this observation.

Solution Since the conjugate acid (obtained by protonation at the doubly bonded nitrogen atom) is highly stabilized by resonance (two equivalent resonance structure out of three), the guanidino group of arginine is one of the most strongly basic of all organic groups.



$$R\ddot{N}H\text{—}\overset{\overset{\ddot{N}H}{\|}}{C}\text{—}\ddot{N}H_2 \xrightarrow[(-A^{\ominus})]{HA} \left[R\ddot{N}H\text{—}\overset{\overset{\overset{\oplus}{N}H_2}{\|}}{C}\text{—}\ddot{N}H_2 \longleftrightarrow R\ddot{N}H\text{—}\overset{\overset{\ddot{N}H_2}{|}}{C}{=}\overset{\oplus}{N}H_2 \longleftrightarrow R\overset{\oplus}{N}H{=}\overset{\overset{\ddot{N}H_2}{|}}{C}\text{—}\ddot{N}H_2\right]$$

Arginine

($R = \text{—}CH_2CH_2CH_2\underset{\underset{NH_2}{|}}{C}HCO_2H$)

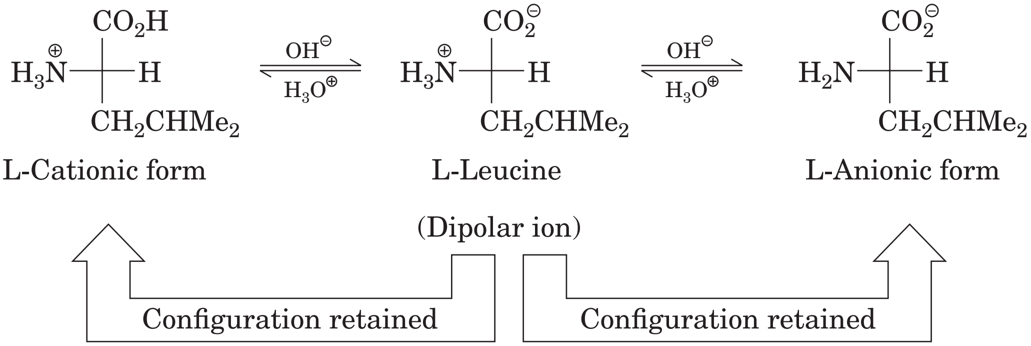
Conjugate acid

(resonance-stabilized)

11. Explain why the specific rotation, $[\alpha]_D^{25}$, an amino acid is pH dependent. Is there any change of absolute configuration of the amino acid with change in the pH of the medium?

Solution Because of different polarisability of various groups, they differ in their optical rotatory power. Therefore, the optical rotatory power of an amino (—NH_2) group and an aminium ($—\overset{\oplus}{N}H_3$) group are different. The same is true for a carboxyl (—CO_2H) group and a carboxylate ($—CO_2^{\ominus}$) group. As a consequence, the specific rotation of the dipolar ion or zwitterion and those of the cationic form ($H_3\overset{\oplus}{N}CARCO_2H$) and the anionic form ($H_2NCHRCO_2^{\ominus}$) are different. Since the concentrations of these three forms are different at different pHs, an amino acid exhibits different specific rotations at different pHs, i.e., the specific rotation, $[\alpha]_D^{25}$, of an amino acid is pH dependent.

Although the specific rotation of an amino acid changes with changes in pH of the medium, the configuration of the chiral centre remains unchanged because no bond to the chiral centre breaks with changes in pH. For example:



12. **Comment on the nature of the medium (acidic or basic) required to speed up esterification and acylation of an amino acid.**

Solution In strongly acidic solution, the cationic form $\overset{\oplus}{N}H_3CHRCOOH$, which contains a free —COOH group, remains as the major species. Therefore, to speed up the esterification of an amino acid, the reaction is to be carried out in strongly acidic solutions. On the other hand, to speed up acylation, it is to be carried out in strongly alkaline solutions where the major species, $H_2NCHRCO_2^{\ominus}$, contains a free —NH_2 group.

13. **In quite alkaline solution, an amino acid contains two basic groups, $—CO_2^{\ominus}$ and $—\ddot{N}H_2$. Which one of these two is expected to be more basic and why? Give the product of protonation of the species containing these two groups.**

Solution The unshared electron pairs on oxygen is delocalized in $—CO_2^{\ominus}$ but the unshared electron pair on nitrogen in $—\ddot{N}H_2$ is localized and readily available to proton. Therefore, the —NH_2 group is more basic than the $—CO_2^{\ominus}$ group. This agrees with their K_b values.

For NH_2, $K_b \simeq 10^{-4}$ and for $—CO_2^{\ominus}$, $K_b = \dfrac{K_W}{K_a} = \dfrac{10^{-4}}{\simeq 10^{-3}} \simeq 10^{-11}$

Therefore, the product of simple protonation of $H_2\ddot{N}CHRCO_2^{\ominus}$ is $H_3\overset{\oplus}{N}CHRCO_2^{\ominus}$.

14. In quite acidic solution, an amino acid contains the two acidic groups, —COOH and $—\overset{\oplus}{N}H_3$. Which one of these two is expected to be more acidic and why? Give the product obtained when base is added to the species containing these two groups.

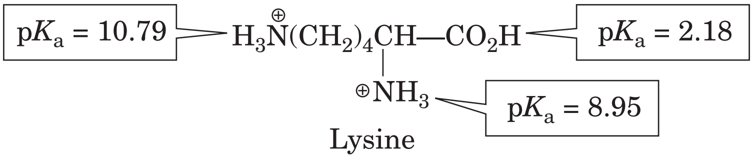
Solution Because of strong electron-attracting inductive effect (–I) of the iminium ($—\overset{\oplus}{N}H_3$) group, the —COOH group is more acidic. This agrees with their K_a values.

For —COOH, $K_a \simeq 10^{-3}$ and for $—\overset{\oplus}{N}H_3$, $K_a = \dfrac{K_W}{K_b} = \dfrac{10^{-14}}{\simeq 10^{-4}} \simeq 10^{-10}$

Therefore, the —COOH group will give up proton readily as base is added to the species $H_3\overset{\oplus}{N}CHRCO_2H$. Hence, the product is $H_3\overset{\oplus}{N}CHRCO_2^{\ominus}$ (the dipolar ion).

15. (a) Draw the form in which lysine predominantly exists in a solution with following pH:

(i) pH = 0 (ii) pH = 4 (iii) pH = 9.87 (iv) pH = 12

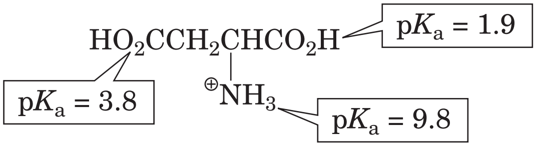


$H_3\overset{\oplus}{N}(CH_2)_4\underset{\oplus NH_3}{CH}—CO_2H$

Lysine

(b) Draw the form in which aspartic acid predominantly exists in a solution with the following pH:

(i) pH = 1 (ii) PH = 2.85 (iii) pH = 6 (iv) pH = 11.5

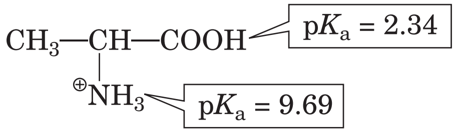


$HO_2CCH_2\underset{\oplus NH_3}{CH}CO_2H$

Aspartic acid

(c) Draw the form in which alanine predominantly exists in a solution with the following pH:

(i) pH = 0 (ii) pH = 6.02 (iii) pH = 12

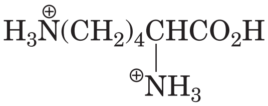


$$CH_3-\underset{\substack{| \\ \overset{\oplus}{N}H_3}}{C}H-COOH$$

Alanine

Solution

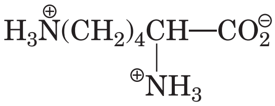
(a) (i) The protonated amino groups and also the carboxyl group will remain in their acid forms because the pH of the solution is less than their pK_a values. That is, at pH = 0, lysine exists in the following form:



$$H_3\overset{\oplus}{N}(CH_2)_4\underset{\substack{| \\ \overset{\oplus}{N}H_3}}{C}HCO_2H$$

(at pH = 0)

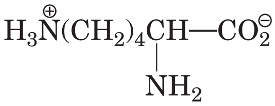
(ii) Both the protonated amino group will remain in their acid forms because the pH of the solution (pH = 4) is less than their pK_a values. On the other hand, the carboxyl group will remain in its basic form because its pK_a is less than the pH of the solution. Therefore, at pH = 4, lysine exists in the following form:



$$H_3\overset{\oplus}{N}(CH_2)_4\underset{\substack{| \\ \overset{\oplus}{N}H_3}}{C}H-CO_2^{\ominus}$$

(at pH = 4)

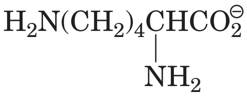
(iii) The protonated α-$\overset{\oplus}{N}H_3$ group and the —COOH group will remain in their basic form because the pH of the solution (pH = 9.87) is greater than their pK_a values. On the other hand, the other protonated amino group will remain in acidic form because its pK_a is greater than the pH of the solution. Therefore, the form in which lysine exists in a solution with pH = 9.87 is:



$$H_3\overset{\oplus}{N}(CH_2)_4\underset{\substack{| \\ NH_2}}{C}H-CO_2^{\ominus}$$

(at pH = 9.87)

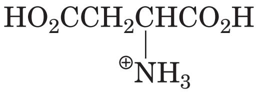
(iv) Both the protonated amino groups and the carboxyl group will remain in their basic forms because the pH of the solution (pH = 12) is greater than their pK_a values. Therefore, at pH = 12, lysine exists in the following form:



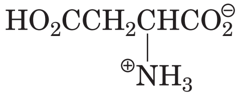
$$H_2N(CH_2)_4\underset{\substack{| \\ NH_2}}{C}HCO_2^{\ominus}$$

(at pH = 12)

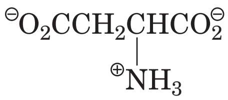
(b) Different forms of aspartic acid:

(i)

$HO_2CCH_2\underset{{}^{\oplus}NH_3}{\underset{|}{C}}HCO_2H$

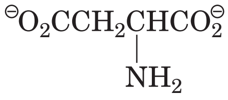
(at pH = 1)

(ii)

$HO_2CCH_2\underset{{}^{\oplus}NH_3}{\underset{|}{C}}HCO_2^{\ominus}$

(at pH = 2.85,
i.e., at p*I*)

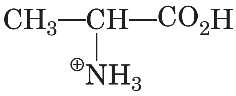
(iii)

${}^{\ominus}O_2CCH_2\underset{{}^{\oplus}NH_3}{\underset{|}{C}}HCO_2^{\ominus}$

(at pH = 6)

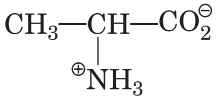
(iv)

${}^{\ominus}O_2CCH_2\underset{NH_2}{\underset{|}{C}}HCO_2^{\ominus}$

(at pH = 11.5)

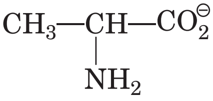
(c) Different forms of alanine:

(i)

$CH_3—\underset{{}^{\oplus}NH_3}{\underset{|}{C}}H—CO_2H$

(at pH = 0)

(ii)

$CH_3—\underset{{}^{\oplus}NH_3}{\underset{|}{C}}H—CO_2^{\ominus}$

(at pH = 6.02)

(iii)

$CH_3—\underset{NH_2}{\underset{|}{C}}H—CO_2^{\ominus}$

(at pH = 12)

16. Identify the amino acid which has: (a) the lowest p*I* value, (b) the highest p*I* value (c) the greatest amount of negative charge at pH 6.20 and (d) a greater negative charge at pH 6.0: glycine or methionine.

Solution

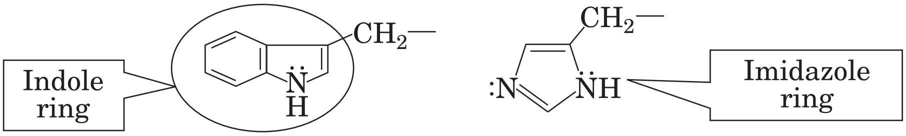
(a) Aspartic acid, $HO_2C\ CH_2CH(NH_2)\ CO_2H$, has the lowest p*I* value, (b) arginine, $HN{=}C(NH_2)NH(CH_2)_3CH(NH_2)CO_2H$, has the highest p*I* value, (c) aspartic acid, and (d) methionine.

17. In an alkaline solution alanine, $H_2\ddot{N}CH(CH_3)CO_2^{\ominus}$, has two basic groups. Write the forms of alanine obtained when 1 and 2 equivalents of acid are added, respectively.

Solution The $–\ddot{N}H_2$ group is more basic than the $–CO_2^{\ominus}$ group and because of this, the form of alanine obtained on addition of 1 equivalent of acid is $H_3\overset{\oplus}{N}CH(CH_3)CO_2^{\ominus}$ the dipolar ion or zwitterion. Therefore, the form obtained on addition of 2 equivalents of acid is $H_3\overset{\oplus}{N}CH(CH_3)CO_2H$, the cationic form.

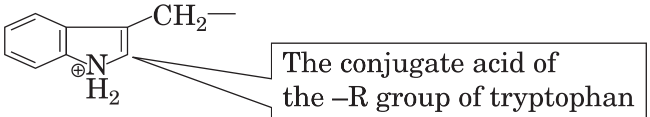
18. Explain why the –R group of tryptophan is very weakly basic than the –R group of histidine.

Solution R- groups of these two amino acids are as follows:

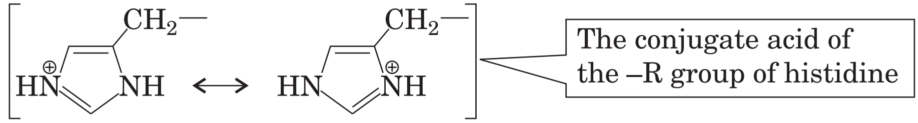


(of tryptophan) (of histidine)

The unshared electron pair on nitrogen of the indole ring is involved in maintaining the aromatic sextet. The N atom is, therefore, very much reluctant to accept a proton by sacrificing aromaticity of the five membered ring. On the other hand, the double-bonded N in the imidazole ring is histidine is much willing to accept a proton because the corresponding conjugate base is highly stabilized by resonance involving two equivalent resonance structures and also the aromaticity is preserved.



(the positive charge is localized and the aromaticity is lost)



(the positive charge is delocalized and the aromaticity of the ring is preserved)

19. Toward which electrode an amino acid, placed in an electric field, would migrate at a (a) pH < p*I*, (b) pH > p*I*, and (c) pH = p*I*? Give your reasoning. [C.U. 2015]

Solution In an aqueous solution, there exists an equilibrium between the dipolar ion or zwitterionic form and the anionic and cationic forms of an amino acid:

$$\overset{\ominus}{O}H + \underset{\text{Cationic form}}{H_3\overset{\oplus}{N}CHRCO_2H} \overset{H_2O}{\rightleftharpoons} \underset{\text{Dipolar ion}}{H_3\overset{\oplus}{N}CHRCO_2^{\ominus}} \overset{H_2O}{\rightleftharpoons} \underset{\text{Anionic form}}{H_2NCHRCO_2^{\ominus}} + H_3O^{\oplus}$$

(a) At a pH lower than its p*I*, the cationic form predominates and therefore, when exposed to an electric field, an amino acid migrates toward the cathode (the negative electrode).

(b) At a pH higher than its p*I*, the anionic form of an amino acid predominates and therefore, when exposed to an electric field, it migrates toward the anode (the positive electrode).

(c) At its p*I*, an amino acid exists predominantly as the dipolar ion having balanced charges and therefore, no net migration occurs when placed in an electric field.

20. Define the isoelectric point of an amino acid. How would you separate glycine (p*I* = 6.0) from lysine (p*I* = 9.8) by electrophoresis?

[C.U. 2011, 2014]

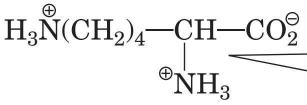
Solution See **article no. 10.1.4.**

An aqueous solution of the mixture of the two amino acids is placed on a filter paper (the supporting medium) and subjected to an electric field. The pH is adjusted to either 6.0 or 9.8. At pH = 6.0, glycine does not migrate but lysine migrates to the cathode. At pH = 9.8, lysine does not migrate while glycine migrates to the anode.

Zwitterionic form

$H_2\overset{\oplus}{N}CH_2CO_2^{\ominus}$

Glycine
(at pH = 6)



$H_3\overset{\oplus}{N}(CH_2)_4—\underset{\overset{|}{{}^{\oplus}NH_3}}{CH}—CO_2^{\ominus}$

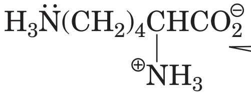
Lysine
(at pH = 6)

Cationic form that migrates to cathode

$H_2\ddot{N}CH_2CO_2^{\ominus}$

Glycine
(at pH = 9.8)

Anionic form that migrates to anode



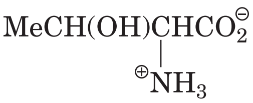
$H_3\ddot{N}(CH_2)_4\underset{\overset{|}{{}^{\oplus}NH_3}}{C}HCO_2^{\ominus}$

Lysine
(at pH = 9.8)

Zwitterionic form

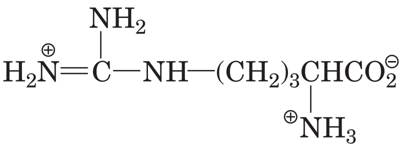
21. What is the suitable pH for separating a mixture of glutamic acid (p*I* = 3.2), arginine (p*I* = 10.8) and threonine (p*I* = 6.5) by electrophoresis? Give your reasoning.

Solution The suitable pH for separating a mixture of glutamic acid, arginine and threonine is 6.5. This is because at this pH, threonine has zero net charge and does not migrate to any electrode, glutamic acid (p*I* = 3.2) ios converted to its anionic form, and migrates to the anode and arginine (p*I* = 10.8) is converted to its cationic form, and migrates to the cathode.



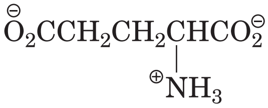
$MeCH(OH)\underset{\overset{|}{{}^{\oplus}NH_3}}{C}HCO_2^{\ominus}$

Threonine
(dipolar ion at
pH = 6.5)



$H_2\overset{\oplus}{N}=\overset{\overset{NH_2}{|}}{C}—NH—(CH_2)_3\underset{\overset{|}{{}^{\oplus}NH_3}}{C}HCO_2^{\ominus}$

Arginine
(cationic form at
pH = 6.5)

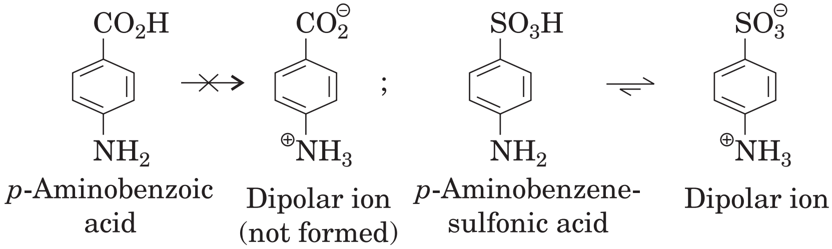


$\overset{\ominus}{O}_2CCH_2CH_2\underset{\overset{|}{{}^{\oplus}NH_3}}{C}HCO_2^{\ominus}$

Glutamic acid
(anionic form at
pH = 6.5)

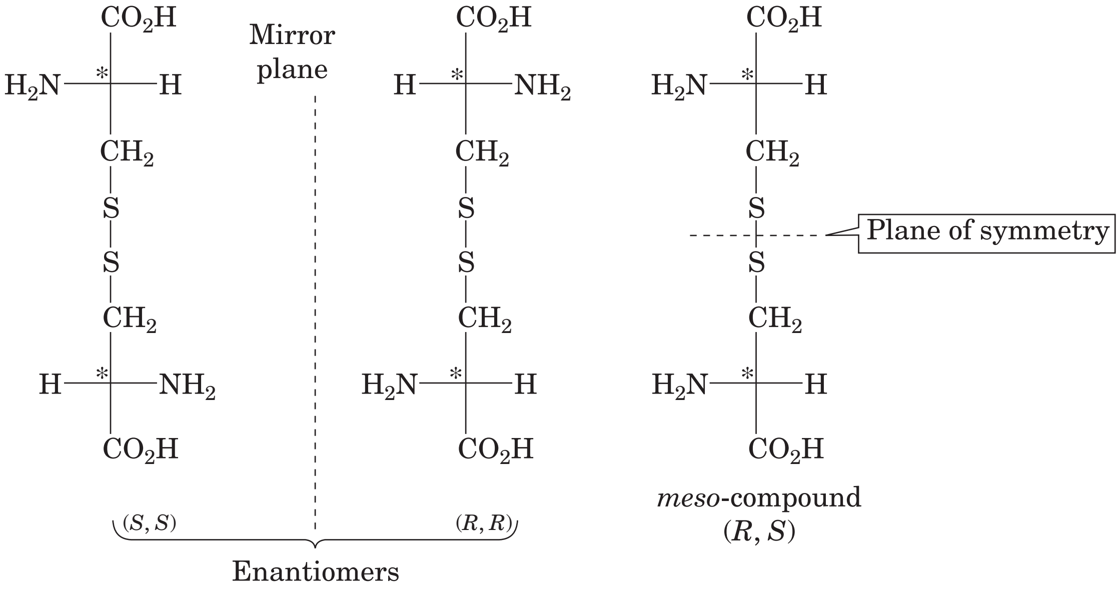
22. *p*-Aminobenzoic acid (p-$H_2NC_6H_4CO_2H$) does not exist as the dipolar ion zwitterion, whereas *p*-aminobenzenesulfonic acid (p-$H_2NC_6H_4SO_3H$) does. Explain this observation.

Solution K_b for the aromatic $-NH_2$ group ($\sim 10^{-10}$) is somewhat lower than the K_b for the $-CO_2^{\ominus}$ group ($\sim 10^{-9}$). Therefore, the $-CO_2^{\ominus}$ group is slightly more basic than the aromatic $-NH_2$ group. As a result, the $-NH_2$ group is not neutralized by the internal $-CO_2H$ group. Since the $-SO_3H$ group is strongly acidic, it can neutralize an aromatic $-NH_2$ group. For this reason, *p*-aminobenzoic acid does not exist appreciably as the dipolar ion, but *p*-aminobenzenesulfonic acid (sulphanilic acid) does.



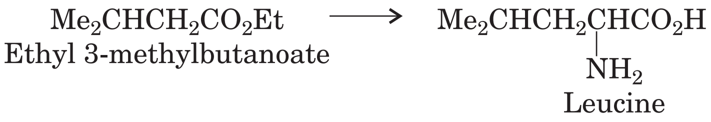
23. Comment on the stereoisomers of the amino acid cystine (Cys-Cys).

Solution The amino acid cystine (Cys-Cys) contains two similar asymmetric carbons. Therefore, it exists as two optically active isomers and one optically inactive *meso*-compound. Fischer projections of these three stereoisomers are shown below:



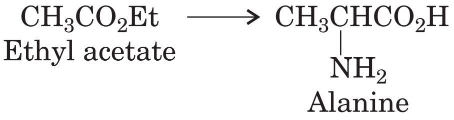
24. How would you carry out the following transformations using reductive amination in one of the steps?

(a)



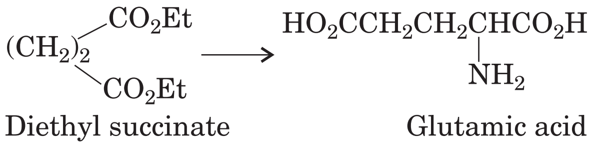
$$\underset{\text{Ethyl 3-methylbutanoate}}{\mathrm{Me_2CHCH_2CO_2Et}} \longrightarrow \underset{\text{Leucine}}{\mathrm{Me_2CHCH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCO_2H}}$$

(b)



$$\underset{\text{Ethyl acetate}}{\mathrm{CH_3CO_2Et}} \longrightarrow \underset{\text{Alanine}}{\mathrm{CH_3\underset{\displaystyle NH_2}{\underset{|}{C}}HCO_2H}}$$

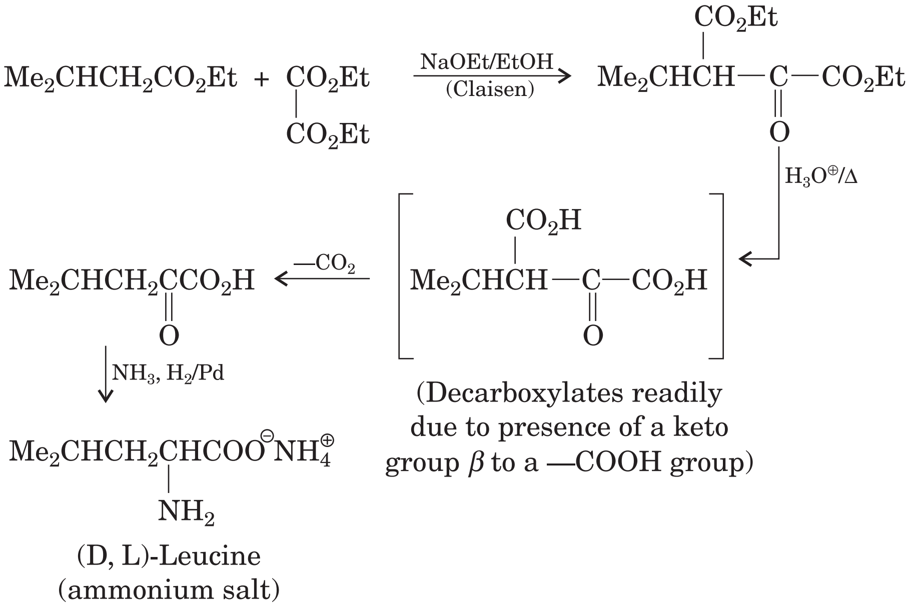
(c)



$$\underset{\text{Diethyl succinate}}{\mathrm{(CH_2)_2(CO_2Et)_2}} \longrightarrow \underset{\text{Glutamic acid}}{\mathrm{HO_2CCH_2CH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCO_2H}}$$

Solution

(a)



$$\mathrm{Me_2CHCH_2CO_2Et} + \mathrm{\underset{\displaystyle CO_2Et}{\underset{|}{CO_2Et}}} \xrightarrow[\text{(Claisen)}]{\text{NaOEt/EtOH}} \mathrm{Me_2CH\overset{\displaystyle CO_2Et}{\overset{|}{C}H}-\underset{\displaystyle O}{\underset{\|}{C}}-CO_2Et}$$

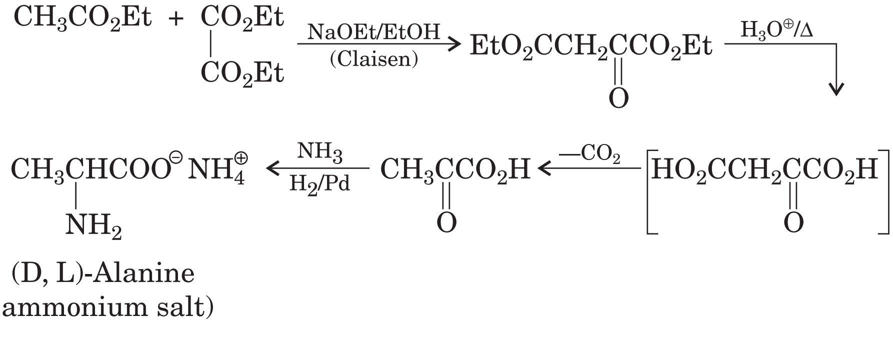
$$\xrightarrow{\mathrm{H_3O^{\oplus}/\Delta}} \left[\mathrm{Me_2CH\overset{\displaystyle CO_2H}{\overset{|}{C}H}-\underset{\displaystyle O}{\underset{\|}{C}}-CO_2H}\right] \xrightarrow{-\mathrm{CO_2}} \mathrm{Me_2CHCH_2\underset{\displaystyle O}{\underset{\|}{C}}CO_2H}$$

$$\xrightarrow{\mathrm{NH_3,\ H_2/Pd}} \mathrm{Me_2CHCH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCOO^{\ominus}\,NH_4^{\oplus}}$$

(Decarboxylates readily due to presence of a keto group β to a —COOH group)

(D, L)-Leucine (ammonium salt)

(b)

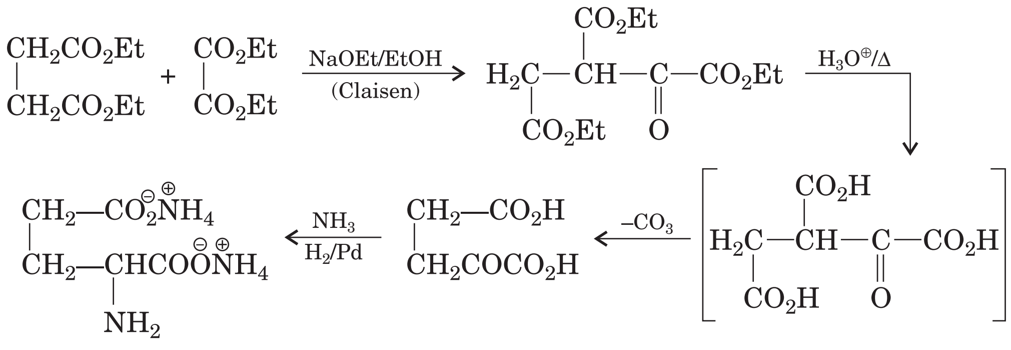


$$\mathrm{CH_3CO_2Et} + \mathrm{\underset{\displaystyle CO_2Et}{\underset{|}{CO_2Et}}} \xrightarrow[\text{(Claisen)}]{\text{NaOEt/EtOH}} \mathrm{EtO_2CCH_2\underset{\displaystyle O}{\underset{\|}{C}}CO_2Et} \xrightarrow{\mathrm{H_3O^{\oplus}/\Delta}} \left[\mathrm{HO_2CCH_2\underset{\displaystyle O}{\underset{\|}{C}}CO_2H}\right]$$

$$\xrightarrow{-\mathrm{CO_2}} \mathrm{CH_3\underset{\displaystyle O}{\underset{\|}{C}}CO_2H} \xrightarrow[\mathrm{H_2/Pd}]{\mathrm{NH_3}} \mathrm{CH_3\underset{\displaystyle NH_2}{\underset{|}{C}}HCOO^{\ominus}\,NH_4^{\oplus}}$$

(D, L)-Alanine (ammonium salt)

(c)

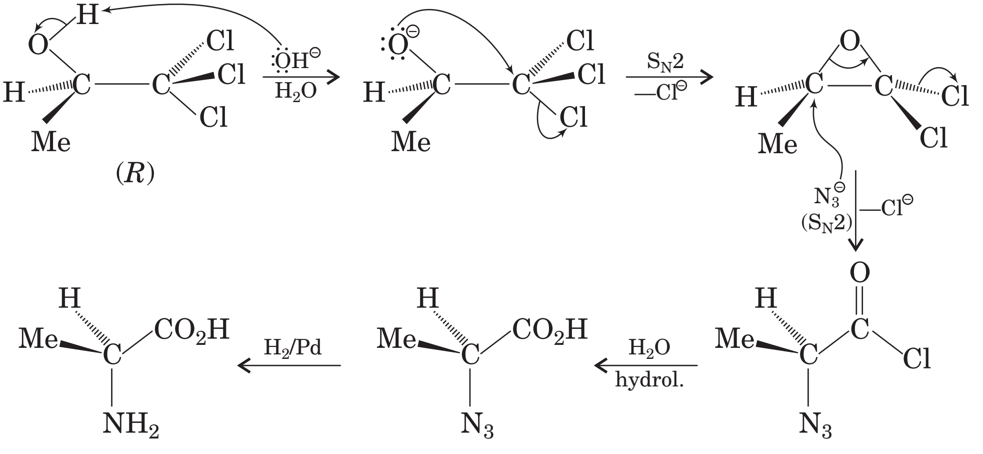


(D, L)-Glutamic acid
(ammonium salt)

25. How would you prepare (*S*)-alanine from (a) (*R*)-MeCH(OH)CCl_3 and (b) (*S*)-serin?

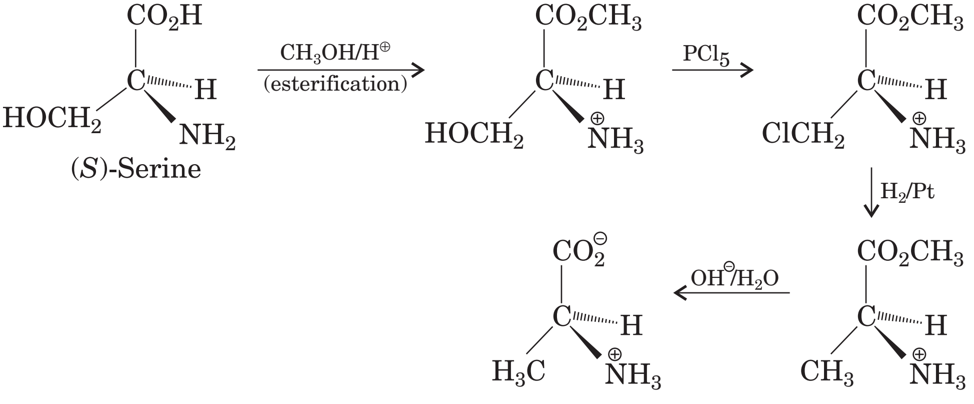
Solution

(a) When (*R*)-MeCH(OH)CCl_3 is treated with alkaline solution of NaN_3 and the product is reduced with H_2/Pd, (*S*)-alanine is obtained.



(*S*)-Alanine

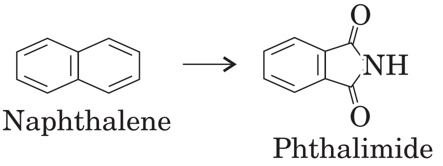
(b)



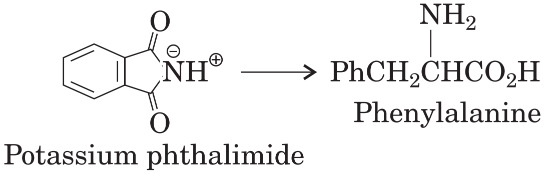
(*S*)-Alanine

26. How would you carry out the following transformations?

(a)



(b)

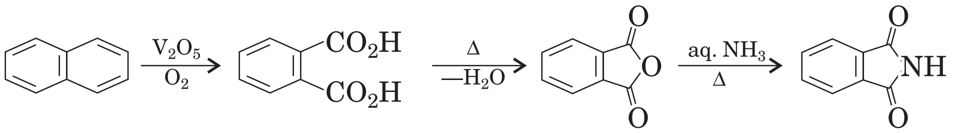


(*Gabriel phthalimide synthesis*)

(C.U. 2013)

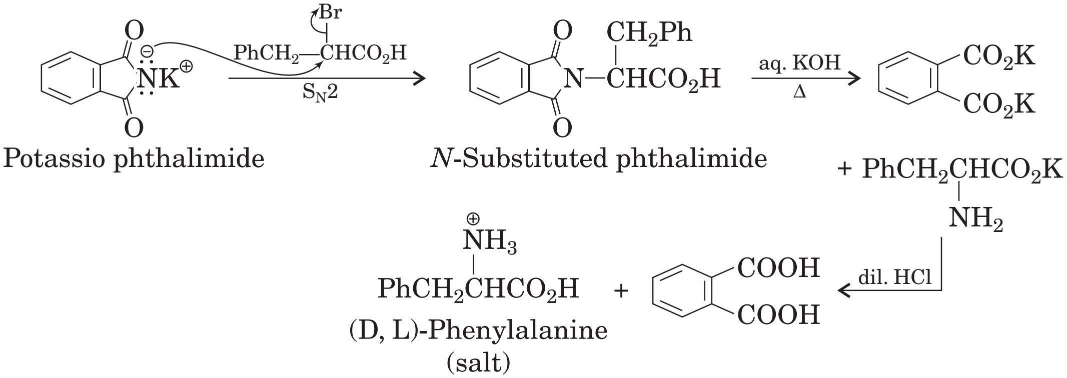
Solution

(a)



Phthalimide
(with ethanolic KOH
it forms potassium salt)

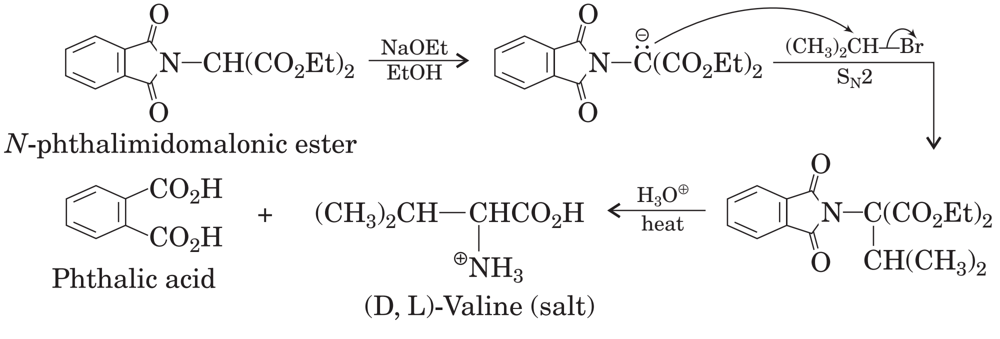
(b)



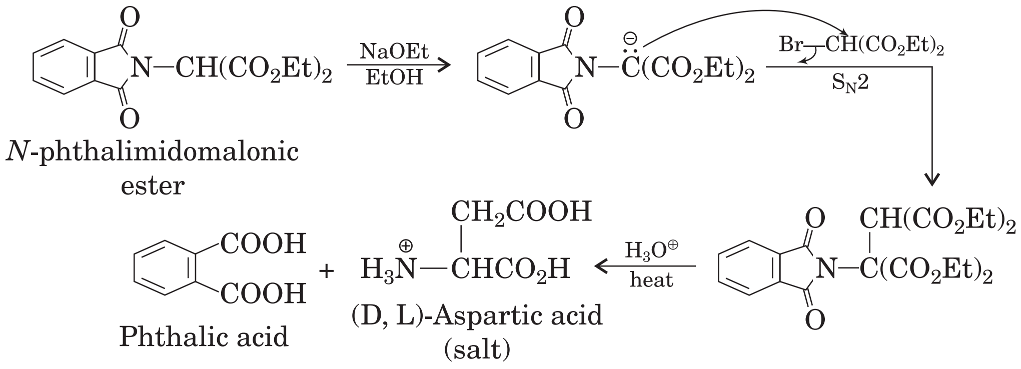
27. Show how Gabriel-malonic ester synthesis could be used to make (a) valine, (b) aspartic acid and (c) methionine.

Solution

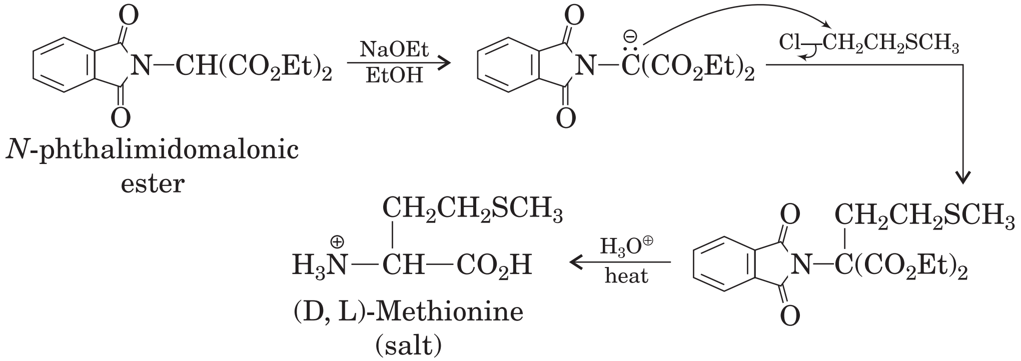
(a)



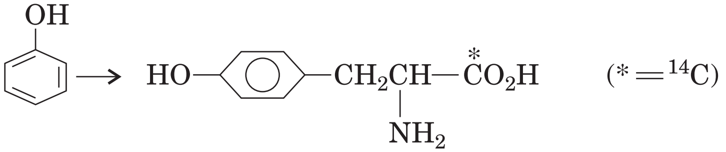
(b)



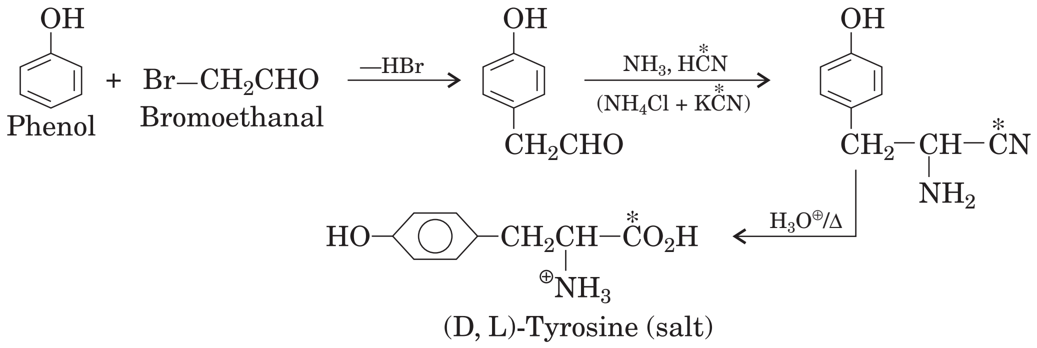
(c)



28. How would you carry out the following transformation involving Strecker synthesis?

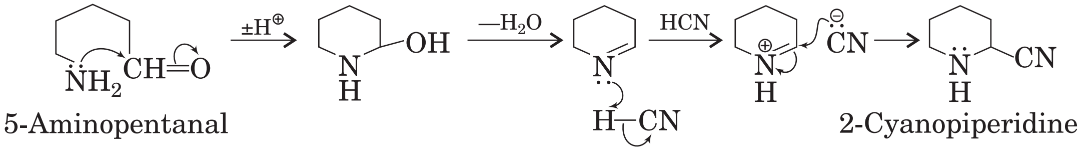


Solution The labelled tyrosine may be prepared as follows:



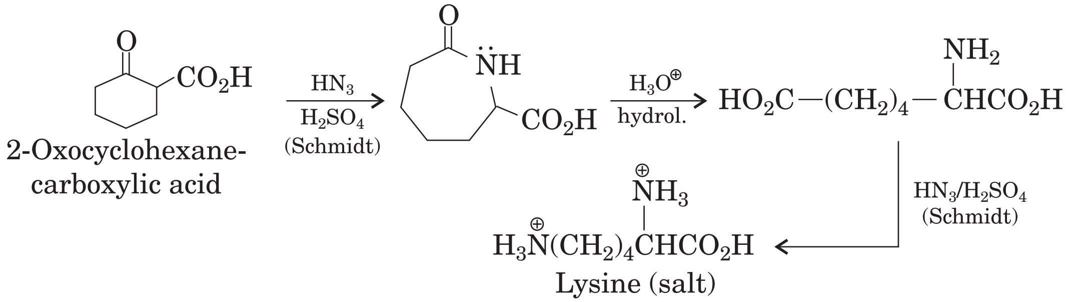
29. What problem arises in application of Strecker synthesis for the synthesis of lysine?

Solution For the preparation of lysine, $H_2N(CH_2)_4CH(NH_2)CO_2H$, using Strecker synthesis, an aldehyde like $H_2N(CH_2)_4$ CHO is required and the preparation of this compound in stable form is difficult because it readily forms a six-membered nitrogenous heterocycle by an intramolecular addition reaction followed by loss of water. The resulting compound undergoes nucleophilic addition of HCN to form 2-cyanopiperidine. The reaction sequence may be shown as follows:



30. Prepare lysine from 2-oxocyclohexanecarboxylic acid using the Schmidt reaction? Give the reactions involved.

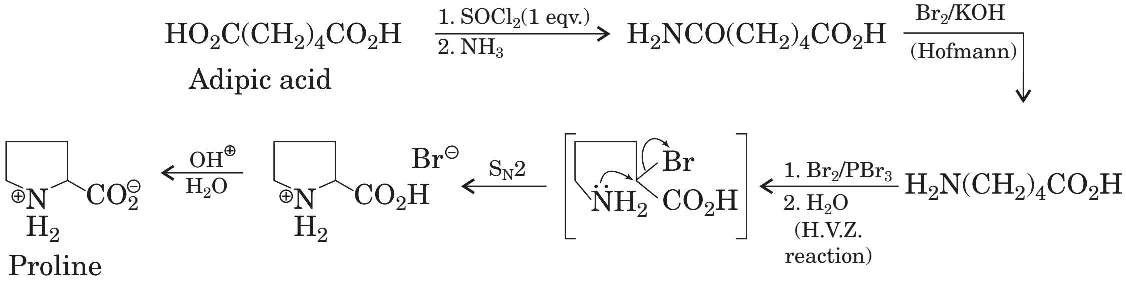
Solution When 2-oxocyclohexanecarboxylic acid is subjected to two consecutive Schmidt reactions, lysine is obtained. The reactions may be outlined as follows:



The first Schmidt reaction occurs with the Keto group, whereas the second Schmidt reaction occurs with the carboxyl group.

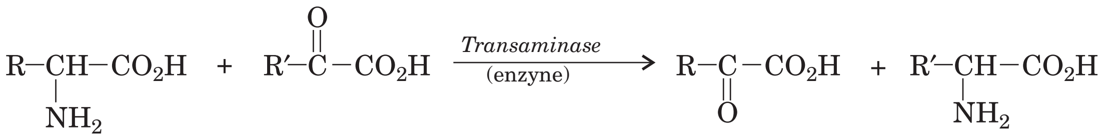
31. Show how would you use a Hofmann rearrangement and an H.V.Z. reaction to propare proline from adipic acid.

Solution



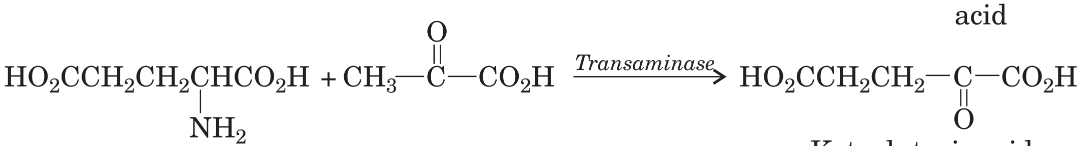
32. What do you mean by transamination? Provide a mechanism for this process. Which amino acids cannot be formed by this process?

Solution Transamination is a biosynthetic process involving transfer of an amino group from an α-amino acid to an α-ketoacid resulting in the formation of a new α-amino acid and a new α-ketoacid. This enzyme catalyzed reaction may be shown as follows:



$$R-\underset{\underset{NH_2}{|}}{CH}-CO_2H + R'-\overset{\overset{O}{\|}}{C}-CO_2H \xrightarrow[\text{(enzyne)}]{\textit{Transaminase}} R-\underset{\underset{O}{\|}}{C}-CO_2H + R'-\underset{\underset{NH_2}{|}}{CH}-CO_2H$$

An α-amino acid An α-ketoacid A new α-ketoacid A new α-amino-acid



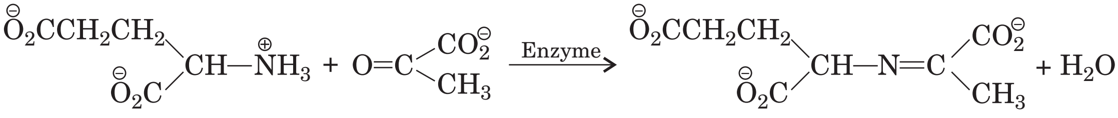
$$\text{e.g., } HO_2CCH_2CH_2\underset{\underset{NH_2}{|}}{C}HCO_2H + CH_3-\overset{\overset{O}{\|}}{C}-CO_2H \xrightarrow{\textit{Transaminase}} HO_2CCH_2CH_2-\underset{\underset{O}{\|}}{C}-CO_2H$$

L-Glutamic acid Pyruvic acid α-Ketoglutaric acid

$+ CH_3CH(NH_2)CO_2H$
L-Alanine

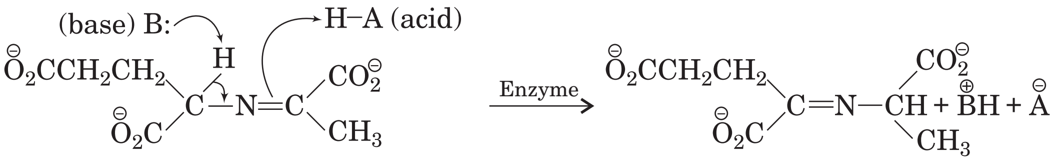
Mechanism The mechanism of transamination involves the steps (enzyme catalyzed) as follows:

Step 1: The amine function of L-glutamate condenses with the α-Keto function of pyruvate to form an imine.



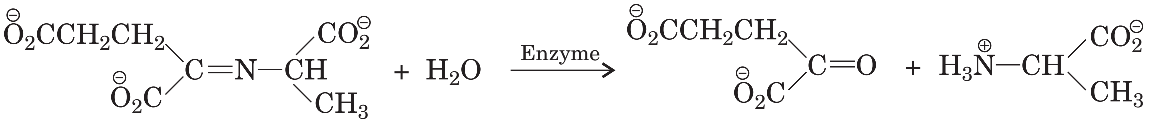
L-Glutamate Pyruvate Imine

Step 2: Proton transfer occurs to form an isomeric imine.



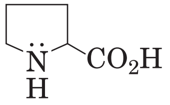
Rearranged imine Rearranged imine

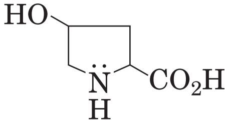
Step 3: The rearranged imine undergoes hydrolysis to form L-alanine and α-ketoglutarate.



Rearranged imine α-Ketoglutarate L-Alanine

Since proline and hydroxyproline have secondary amine function (>NH), they cannot be obtained by the enzyme catalyzed transamination process (only 1° amines can be made this way).


Proline

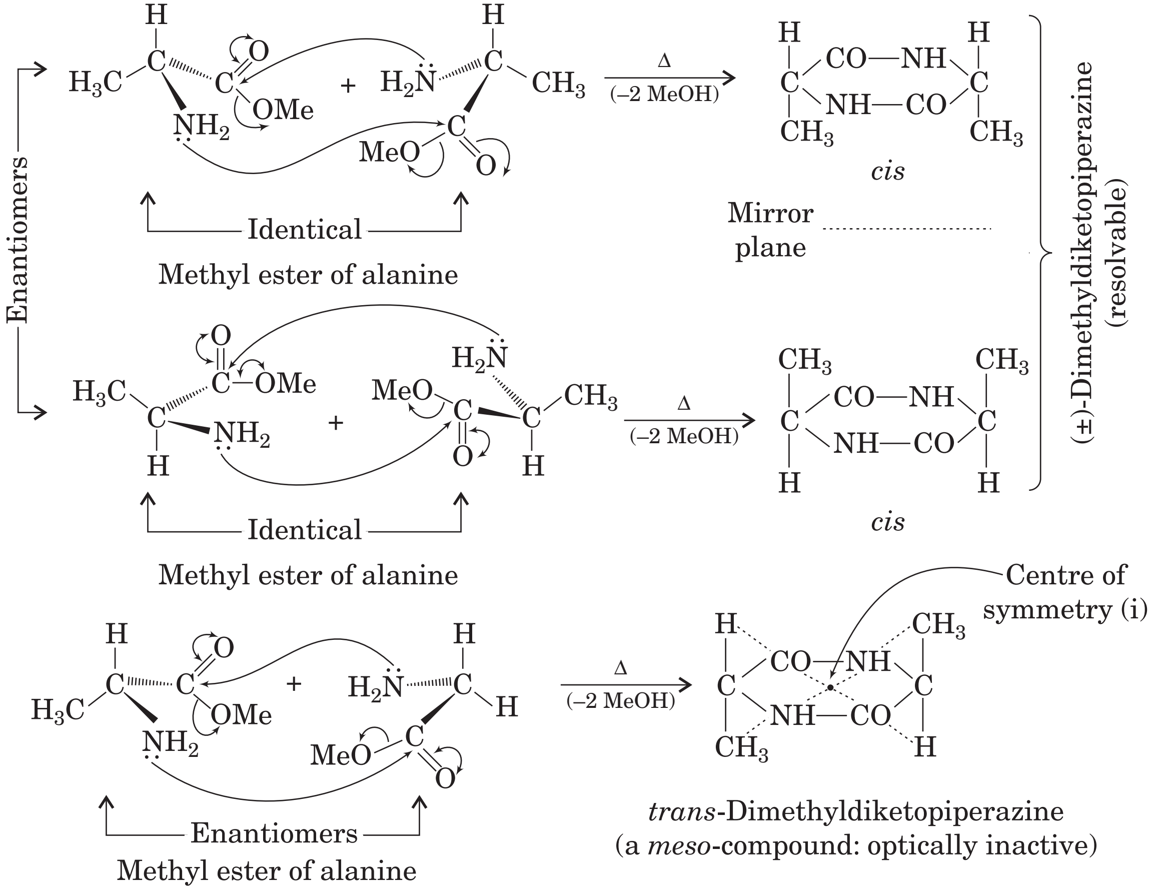

Hydroxyproline

33. Predict the aldehyde expected to be formed when leucine is treated with ninhydrin?

Solution When an α-amino acid, $RCH(HN_2)CO_2H$, is allowed to react with ninhydrin, RCHO is obtained. Therefore, when leucine, $Me_2CHCH_2CH(NH_2)CO_2H$, is treated with ninhydrin, Me_2CHCH_2CHO (3-methylbutanal) is expected to be obtained.

34. When the methyl ester of *rac*-alanine is heated two diastereoisomeric dimethyldiketopiperazines are obtained. One of them cannot be resolved. Give their structures and account for their stereochemistry.

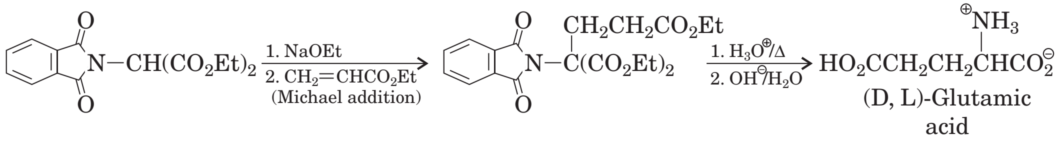
Solution



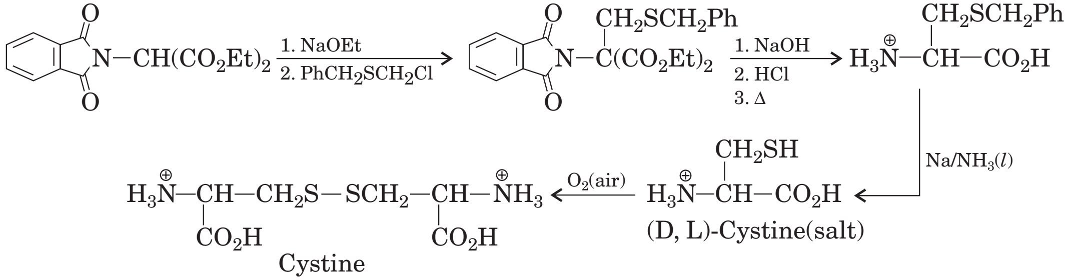
35. Show how the Gabriel-malonic ester synthesis could be used to prepare: (a) glutamic acid (b) cysteine and cystine (c) leucine (d) proline?

Solution

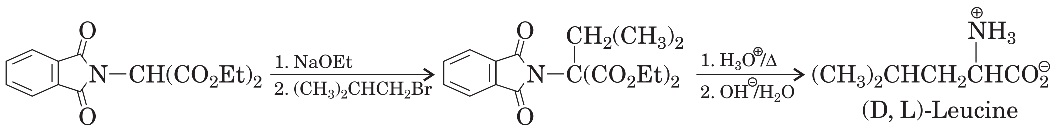
(a)



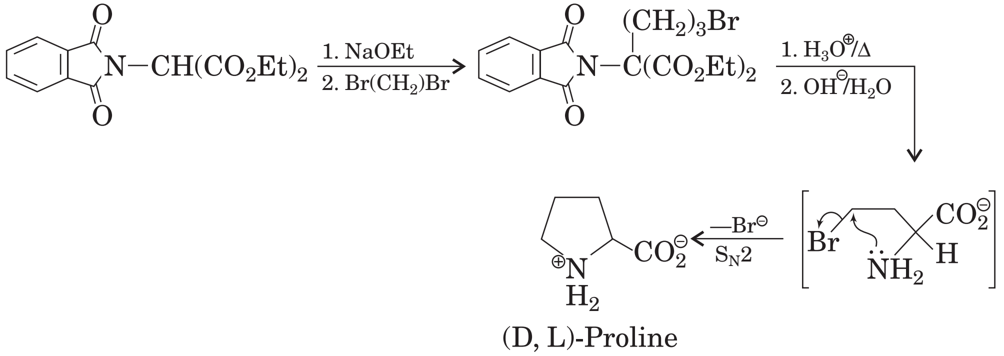
(b)



(c)

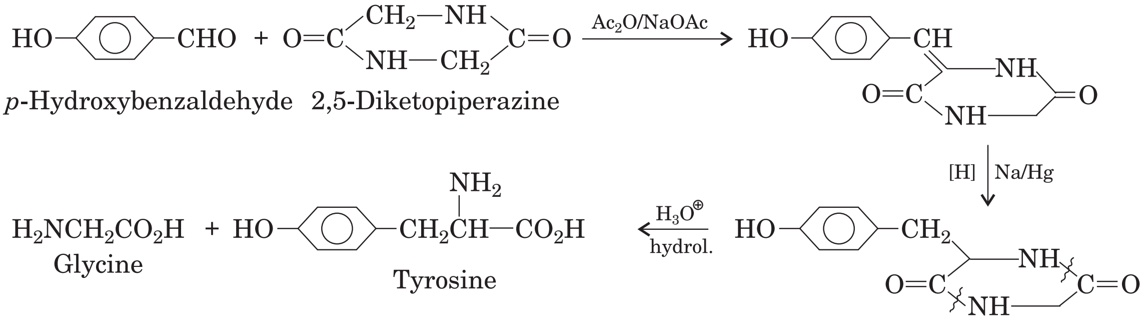


(d)



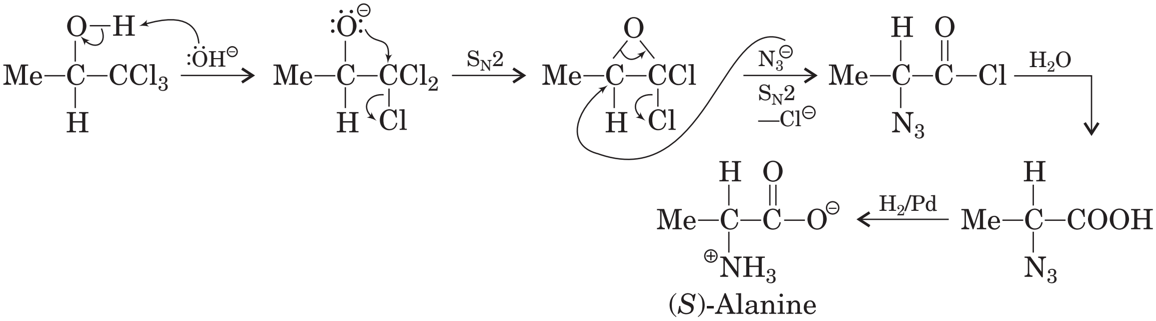
36. Using 2,5-diketopiperazine how would you synthesize tyrosine?

Solution Tyrosine may be synthesized by using *p*-hydroxybenzaldehyde and 2,5-diketopiperazine as follows:



37. When (R)-MeCH(OH)CCl_3 is treated with alkaline NaN_3 followed by H_2/Pd, (*S*)-alanine is obtained. Explain this observation.

Solution In the presence of base, —OH produces —$O^\ominus$ ion which displaces a Cl forming an oxirane ring. The ring is then opened by the azide ion with inversion of configuration (S_N2). Hydrolysis, followed by reduction of the —N_3 group produces (*S*)-alanine.



STUDY PROBLEMS

1. What is meant by an amino acid? Is anthranilic acid an amino acid in true sense of the definition.
2. Classify the amino acids according to their R groups.
3. (a) What is the absolute configuration (*R* or *S*) at α carbon in each of the following amino acids. (i) L-serine (ii) L-methionine
   (b) Why is L-cysteine unique in having *R* configuration?
4. The amino acids found in proteins are assigned to the L-family according to their stereochemistry at C-2. Can they all be assigned the same configuration, *R* or *S* at that carbon atom?
5. Explain why the pK_a of the —$\overset{\oplus}{N}H_3$ group of alanine is lower (9.7) than the pK_a of $CH_3\overset{\oplus}{N}H_3$ (10.63).
6. Explain why amino acids exist as salts.
7. Amino acids exist in different charged forms depending on the pH of the aqueous solution in which they are dissolved. Explain this observation.
8. Give example of two essential amino acids one of which is neutral and the other is basic. Which one between phenylalanine and proline must be obtained from our diet and why?
9. Draw all possible stereoisomeric formulas for the amino acid threonine.
10. Account for the fact that sulphanilic acid dissolves in alkali but not in acids.
11. Suggest a way to separate a mixture of a monoamino monocarboxylic acids, a monoamino dicarboxylic acid and a diamino monocarboxylic acid.

[**Hint:** Separation may be effected by (i) using differential migration at different pH values (electrophoresis), (ii) using differences in solubility at different pH values and (iii) precipitating acidic amino acids as salts of certain bases, and basic amino acids as salts of certain acids.]

12. There are five amino acids that can exist in more than two stereoisomeric forms. (a) Identify them. (b) How many isomers are possible in each case? Indicate enantiomers, diastereoisomers, and any *meso* compound.
[**Hint:** Each of Thr, Hyl, Hyp and Ile exists as two pairs of enantiomers. Cys-Cys exists as one *meso* and one pair of enantiomers.]

13. Explain the following observations:
- (a) Unlike most amines and carboxylic acids, amino acids are insoluble in diethyl ether.
- (b) The indole nitrogen of tryptophan is more weakly basic than one of the imidazole nitrogen of histidine.
- (c) Although glycine is a low-molecular weight organic compound, it melts (decomposes) at a fairly high temperature (232°C).
- (d) The guanidino group of arginine is one of the most strongly basic of all organic groups.
- (e) Solid amino acids conduct electricity.
- (f) The pK_a values of the carboxyl groups of alanine, serin and cysteine differ from each other.
- (g) The isoelectric point of an amino acid is usually the pH of minimum solubility in water of that acid.
- (h) Glycine itself, as a dipolar ion, reacts with HNO_2 to eliminate nitrogen, whereas the ethyl ester of glycine forms ethyl diazoethanoate.

14. In alkaline solution alanine $H_2NCHCH_3CO_2^{\ominus}$, has two basic groups. Predict the products expected to be obtained on addition of 1 and 2 equivalents of acid, respectively.

15. The p*I* of lysine is the average of the pK_a values of its two protonated amino groups. Explain.

16. Explain why the isoelectric point of aspartic acid (2.98) is much lower than that of leucine (5.98).

17. Draw the form in which each of the following amino acids predominantly exists at physiological pH (7.3):
(a) Aspartate (b) Tyrosine (c) Alanine (d) Arginine

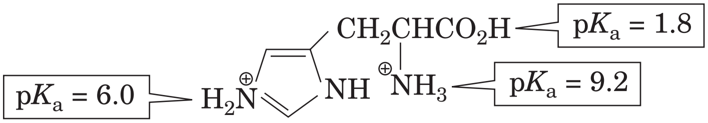
18. Draw the predominant form for glutamate in a solution with the following pH:
(a) 1 (b) 3 (c) 6 (d) 12

[**Hint:** (a) $HO_2CCH_2CH_2CH(\overset{\oplus}{N}H_4)CO_2H$ (b) $HO_2CCH_2CH_2CH(\overset{\oplus}{N}H_4)CO_2^{\ominus}$
(c) $^{\ominus}O_2CCH_2CH_2CH(\overset{\oplus}{N}H_3)CO_2^{\ominus}$ (d) $^{\ominus}O_2CCH_2CH_2CH(NH_2)CO_2^{\ominus}$]

19. Calculate the p*I* of each of the following amino acids:

(a) Iysine (b) Glutamic acid (c) Arginine (d) Serine

20. (a)

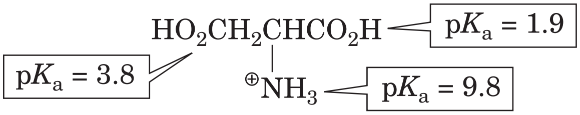


Histidine

Draw the form in which histidine predominantly exists in a solution with the following pH:

(i) pH = 0 (ii) pH = 4 (iii) pH = 8 (iv) pH = 12

(b)



$$HO_2CH_2\underset{\overset{|}{^{\oplus}NH_3}}{C}HCO_2H$$

Aspartic acid

Draw the form in which aspartic acid (p*I* = 3.0) predominantly exists in a solution with the following pH:

(i) pH = 0.5 (ii) pH = p*I* (iii) pH = 7 (iv) pH = 11

21. Explain the following observations:

(a) The pK_a of glutamic acid side chain is greater than the pK_a of aspartic acid side chain.

(b) The pK_a of arginine side chain is greater than the pK_a of lysine side chain.

(c) Amino acids are less acidic than most carboxylic acids and less basic than most amines.

22. Draw the electrophoretic separation of Trp, Cys, and His at pH 6.0.

23. Give the reaction of an α-amino acid (e.g., L-leucine) with ninhydrin and give the plausible mechanism of the reaction. **[C.U. 2011, 2013]**

[**Hint:** See **article no. 10.1.7.**]

24. The following isotropically labelled amino acids are required for biochemical research. How can these be prepared by using $Ba^{14}CO_3$ and $Na^{14}CN$ or $K^{14}CN$ as the only acceptable source of ^{14}C and using D_2O, $LiAlD_4$, or D_2 as the source of deuterium.

(a) $(CH_3)_2CH—CH(NH_2)^{14}CO_2H$ (b) $CH_3{}^{14}CH(NH_2)CO_2H$

(c) $H_2NCD_2(CH_2)_3CH(NH_2)CO_2H$ (d) $^{14}CH_3S(CH_2)_2CH(NH_2)CO_2H$

(e) $HO_2{}^{14}C\ CH_2CH(NH_2)^{14}COOH$

25. Show how the following amino acids might be prepared in the laboratory by reductive amination of the appropriate α-ketoacid:

(a) valine (b) leucine (c) serine (d) glutamine

26. Show how you would use bromination followed by amination to synthesize the following α-amino acids:

(a) glutamic acid (b) valine (c) leucine (d) glycine

27. Conversion of α-ketoacids into α-amino acids in cells occurs by a different mechanism catalyzed by enzyme.

(a) Predict the amino acid obtained from the reductive amination of each of the following metabolic intermediates in a cell. (i) α-ketoglutaric acid (ii) pyruvic acid (iii) oxalacetic acid

(b) What amino acids are formed from these metabolic intermediates when the amino acids are prepared in the laboratory?

[**Hint:** (a) (i) L-Glu, (ii) L-Ala, (iii) L-Asp ; (b) (D, L)-Glu, (D, L)-Ala, and (D, L)-Asp.]

28. Explain why excess ammonia is used when amino acids are prepared from α-bromocarboxylic acids by an S_N2 reaction.

29. What amino acid would be formed when the aldehyde used in the Strecker synthesis is:

(a) 3-methylbutanal (b) ethanal (c) 2-methylpropanal

30. Predict the amino acid expected to be formed when each of the following alkyl halides is used in the 3rd step (an S_N2 reaction) of N-phthalimidomalonic ester synthesis:

(a) $CH_3SCH_2CH_2Cl$ (b) $(CH_3)_2CHCH_2Br$

(c) $PhCH_2Br$ (d) CH_3Br

31. What alkyl halide is to be used in the acetamidomalonic ester synthesis to prepare each of the following α-amino acids?

(a) Phenylalanine (b) Methionine (c) Lysine

32. Suggest how you would separate the free L-amino acid from its acetylated D enantiomer.

33. The enzyme pig lever *esterase* catalyzes the hydrolysis of esters. Esters of L-amino acids are hydrolyzed more rapidly than the esters of D-amino acids. How would this enzyme be used to separate a racemic mixture of amino acids?

34. Carry out the following conversion:

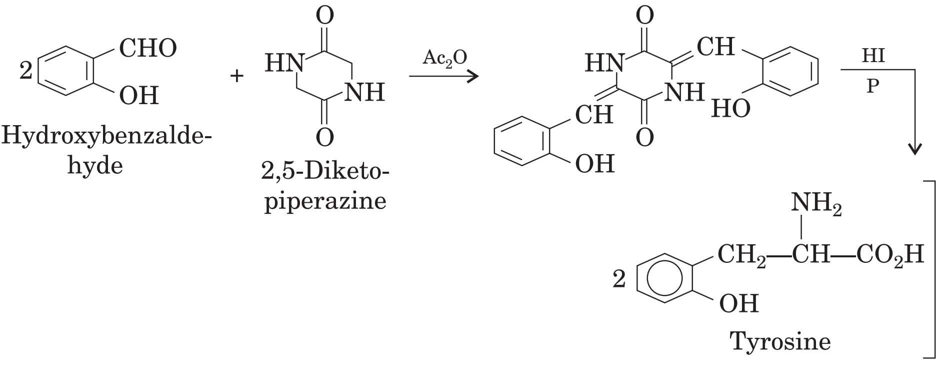
Glycine → Phenylalanine (using Erlenmeyer azalactone syntheses)

[C.U. 2011, 2014]

[**Hint:** See **article no. 10.1.6**]

35. Using 2,5-diketopiperazine, how would you synthesize tyrosine?

[**Hint:**



]

36. Predict the product with mechanism when leucine is heated with acetic anhydride in the presence of pyridine. **[C.U. 2012]**

[**Hint:** See **article no. 10.1.7**]

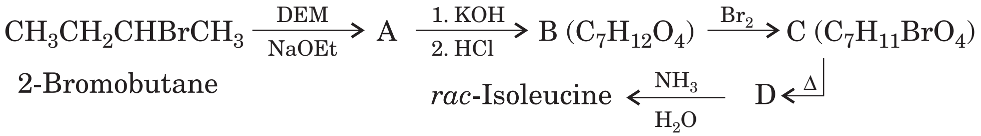
37. Write down the structure of the compound produced by the reaction of one mole of glycine and two moles of ninhydrin. Identify the amino acid which does not give 'Ruhemann's Purple' with ninhydrin. Give justification for your answer. **[C.U. 2015]**

[**Hint:** See **article no. 10.1.7** (ninhydrin reaction). Proline does not give 'Ruhemann's Purple'.]

38. Prepare (i) Leucine and (ii) Tyrosine using diethyl acetamidomalonate. **[C.U. 2015]**

[**Hint:** See **article no. 10.1.6** (acetamidomalonic ester synthesis).]

39. Isoleucine has been prepared by the following sequence of reactions. Predict the structure of compound A through D isolated as intermediates in this synthetic procedure:



40. Alanine has pK_a values of 2.34 (—COOH group) and 9.69 ($—\overset{\oplus}{N}H_3$ group). At what pH will alanine exist in the form indicated below?

(a) $\underset{(50\%)}{H_2NCH_2CO_2^{\ominus}}, \underset{(50\%)}{H_3\overset{\oplus}{N}CH_2CO_2^{\ominus}}$ (b) $\underset{(100\%)}{H_3\overset{\oplus}{N}CH_2CO_2^{\ominus}}$

(c) $\underset{(50\%)}{H_3\overset{\oplus}{N}CH_2CO_2^{\ominus}}, \underset{(50\%)}{H_3\overset{\oplus}{N}CH_2CO_2H}$

[**Hint:** (a) pH = 9.69 ; (b) pH = p*I* = 6.0 ; (c) pH = 2.34]

41. What happens when:

(a) Glutamic acid is heated with EtOH and excess H_2SO_4.
(b) Tyrosine is treated with excess bromine-water.
(c) Proline is allowed to react with methyl iodide.
(d) Serine is heated with excess of acetic anhydride.
(e) Glutamic acid is treated with HNO_2 (1 mole).
(f) Asparagine is heated with aqueous solution of sodium hydroxide.

42. A naturally occurring amino acid form a monoacetyl derivative with excess acetic anhydride, but yields no nitrogen gas when treated with nitrous acid. Suggest a reasonable structure for this amino acid.

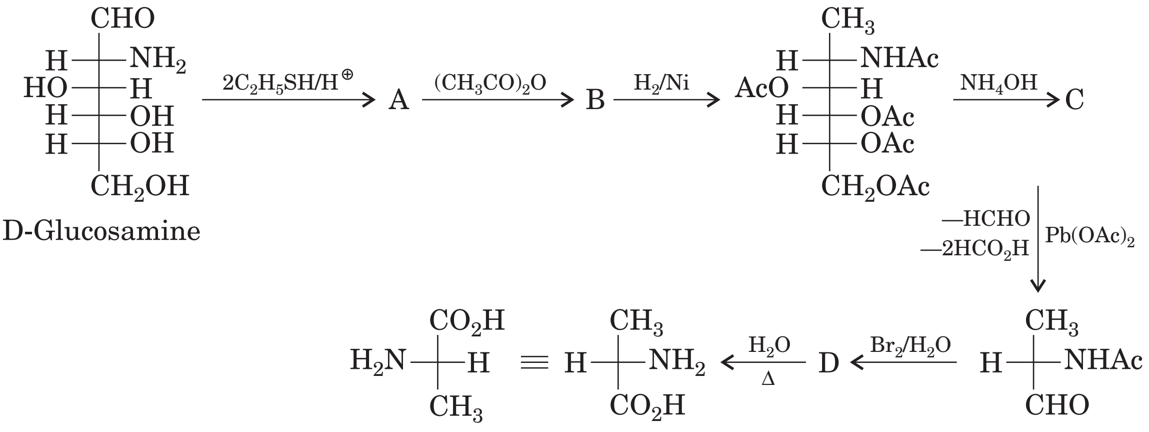
43. (a) All amino acids having a free amino group produces the same purple colour when treated with ninyhydrin—why?

   (b) Use resonance forms to show delocalization of the negative charge in the Ruhemann's purple anion.

44. Show how the following amino acids may be prepared from the indicated method and starting materials:
   (a) glutamic acid from 2-oxopentanedioic acid by the Strecker method
   (b) leucine from 2-methyl-1-propanol by the phthalimidomalonic ester synthesis.
   (c) aspartic acid from ethyl chloroethanoate by the *N*-formylaminomalonic ester synthesis.

45. (a) Draw the structure of the azlactone derived from L-phenylalanine and Ac_2O.
   (b) Which of the hydrogens in this azlactone would you expect to be more acidic?
   (c) Explain why chiral azlactones derived from α-amino acids such as L-phenylalanine racemize easily on heating in the presence of ethanoate ion.

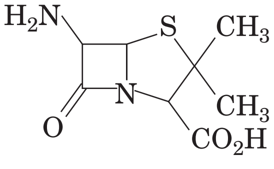
46. The configuration of L-alanine is related to that of D-glucosamine by the following sequence of reactions. Draw the Fischer projection formula for the compounds A—D.



D-Glucosamine

L-Alanine

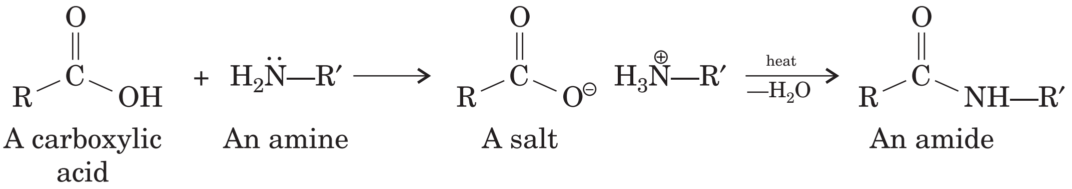
47. Which two α-amino acids are the biosynthetic precursors of penicillin?



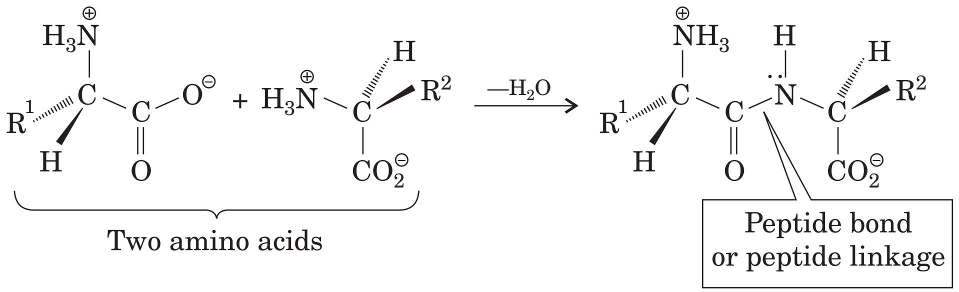
10.2 PEPTIDES

10.2.1 Peptide Linkage

Formation of peptide bonds is the most important reaction of amino acids. Amines and acids can condense, with the loss of water, to form amides. In the laboratory, an amide can be prepared simply by mixing the acid and the amine, and then heating the mixture to eliminate water.

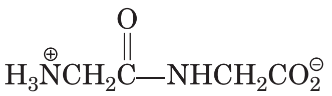


Amides are the most stable acid derivatives. Having both an amino group and a carboxyl group, an amino acid is very suitable to form an amide linkage. Under proper conditions, the amino group of one molecule condenses with carboxyl group of the other. The product is an amide. The amide bond or linkage between the amino acids is called a *peptide bond* or *peptide linkage*.



10.2.2 Classification of Peptides

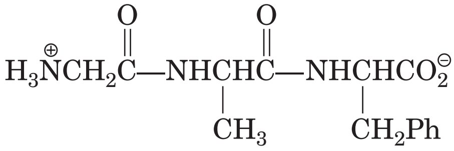
A peptide is any polymer of amino acids linked by amide bonds between the amino group of each amino acid and the carboxyl group of the neighbouring amino acid. Each amino acid unit in the peptide is called a **residue**. If there are two amino acid residues, the peptide is called a **dipeptide**. If there are three amino acid residues, the peptide is called a **tripeptide**. If there are four to ten amino acid residues, the peptide is called an **oligopeptide**. If there are many amino acid residues (less than about 50), the peptide is called a **polypeptide**, and if there are more amino acid residues (50 to > 1000), it is called a **polypeptide** (molecular mass ranges from about 6000 to about 40,000,000). For example:

A dipeptide:


$$H_3\overset{\oplus}{N}CH_2\overset{\overset{\displaystyle O}{\|}}{C}—NHCH_2CO_2^{\ominus}$$

Glycylglycine
(Gly-Gly)

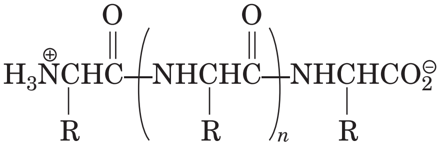
A tripeptide:



$$H_3\overset{\oplus}{N}CH_2\overset{\overset{O}{\|}}{C}—NH\underset{\underset{CH_3}{|}}{C}H\overset{\overset{O}{\|}}{C}—NH\underset{\underset{CH_2Ph}{|}}{C}HCO_2^{\ominus}$$

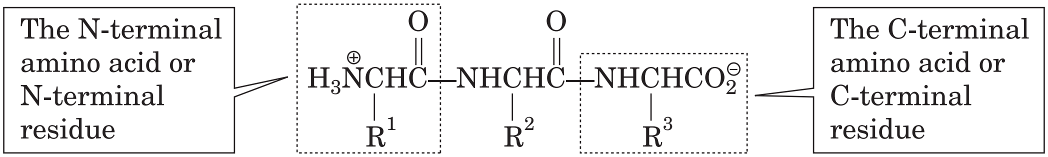
Glycylalanylphenylalanine
(Gly-Ala-Phe)

A polypeptide:



$$H_3\overset{\oplus}{N}\underset{\underset{R}{|}}{C}H\overset{\overset{O}{\|}}{C}\left(NH\underset{\underset{R}{|}}{C}H\overset{\overset{O}{\|}}{C}\right)_n NH\underset{\underset{R}{|}}{C}HCO_2^{\ominus}$$

The end of the peptide with the free amino group ($—\overset{\oplus}{N}H_3$) is called the **N-terminal end** or **N-terminus**, and the end with the free carboxyl group ($—CO_2^{\ominus}$) is called the **C-terminal end** or the **C-terminus**. The two terminal amino acids are called the N-terminal residue and the C-terminal residue, respectively.



$$H_3\overset{\oplus}{N}\underset{\underset{R^1}{|}}{C}H\overset{\overset{O}{\|}}{C}—NH\underset{\underset{R^2}{|}}{C}H\overset{\overset{O}{\|}}{C}—NH\underset{\underset{R^3}{|}}{C}HCO_2^{\ominus}$$

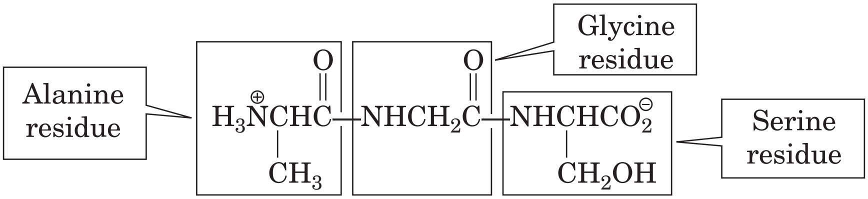
The N-terminal amino acid or N-terminal residue

The C-terminal amino acid or C-terminal residue

A tripeptide

10.2.3 Peptide Nomenclature

By convention, the amino acid residue with the free amino group (the N-terminal residue) is written at the left end and the one with the free carboxyl group (the C-terminal residue) is written at the right end. The suffix *–ine* is replaced by *–yl* for each amino acid in the chain reading from left to right, followed by the full name of the C-terminal residue. The following tripeptide, for example, is named alanylglycylserine. The alanine and the glycine residues have the *–yl* suffix because they have acylated the nitrogen of glycine and serine, respectively.



$$H_3\overset{\oplus}{N}\underset{\underset{CH_3}{|}}{C}H\overset{\overset{O}{\|}}{C}—NHCH_2\overset{\overset{O}{\|}}{C}—NH\underset{\underset{CH_2OH}{|}}{C}HCO_2^{\ominus}$$

Glycine residue

Alanine residue

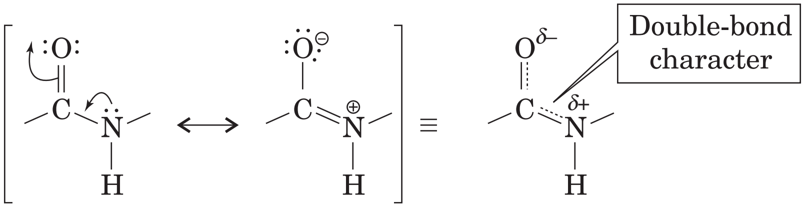
Serine residue

Alanylglycylserine
(Ala-Gly-Ser)

A shorthand system is more convenient, representing each amino acid by its three-letter abbreviation. Once again, the amino acids are arranged from the N terminus at the left to the C terminus at the right. The above tripeptide has the abbreviated name: Aly-Gly-Ser. Single-letter symbols are becoming widely used as well. Thus, the above tripeptide can also be symbolized by AGS.

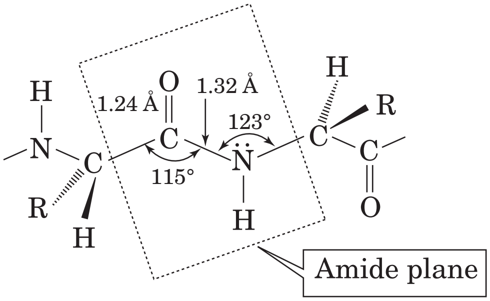
10.2.4 Geometry of the Peptide Linkage

Because of effective resonance interaction between the nonbonding electrons on nitrogen and the carbonyl group, the carbon-nitrogen bond possesses some double-bond character.


Double-bond character

Resonance in peptide linkage Resonance hybrid

In a peptide, this partial double bond character results in six atoms being held rather rigidly in a plane.



Amide plane

Geometry of the peptide linkage

X-ray studies on a number of crystalline peptides indicate that the entire amide group is flat, i.e., the carbonyl carbon, nitrogen, and the atoms attached to them lie in a plane and O and H atoms, are *trans* to each other. Again, the peptide C—N bond (1.32 Å) is shorter in length and stronger than the usual C—N bond (1.47 Å). This indicates that the carbon—nitrogen bond has considerable double-bond character (about 50%). Because of this, the C—N bond has restricted rotation which permits the possibility of geometrical isomerism, the *trans*-isomer being the more likely due to much larger steric interaction operating in the *cis*-isomer.

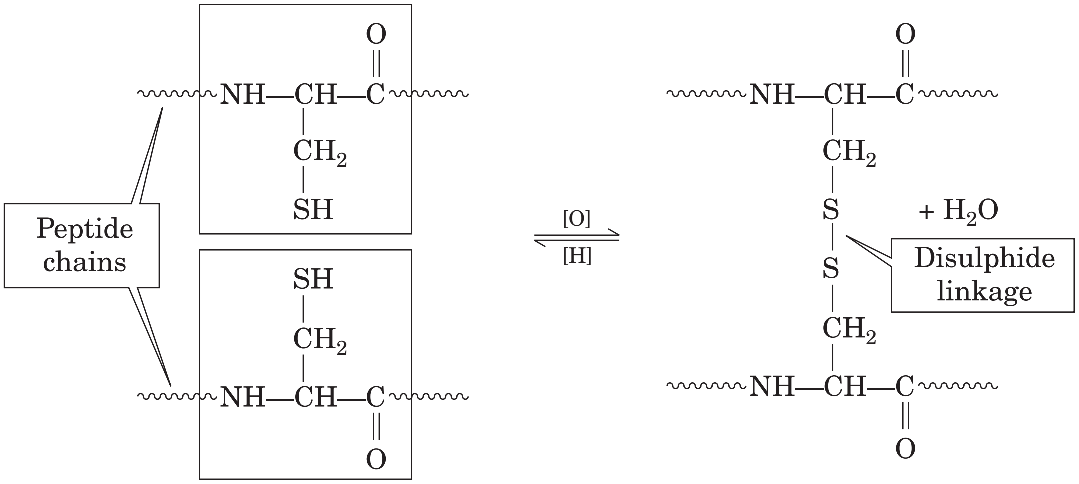
10.2.5 Disulphide Linkages

Amide linkages (peptide linkages) from backbone of the amino acid chain present in peptides and proteins. A second type of covalent bond is possible between any cysteine residue present. Cysteine residues can form disulphide bridges or disulphide linkages which can join two chains or link a single chain into a ring. Two molecules of a thiol form a disulphide linkage by mild oxidation. The reaction is reversible, and a mild reduction breaks the disulphide linkage.

$$\text{R—SH} + \text{HS—R} \xrightleftharpoons[\text{[Reduction]}]{\text{[Oxidation]}} \text{R—S—S—R} + \text{H}_2\text{O}$$

Two thiol molecules A disulphide

Two cysteine sulfhydryl (—SH) groups are oxidized in a similar way to give a disulphide-linked pair of amino acids. This disulphide-linked dimer of cysteine is called *cystine*. The formation of a cystine disulphide bridge linking two peptide chains may be shown as follows:



Two cysteine residues Cystine disulphide bridge

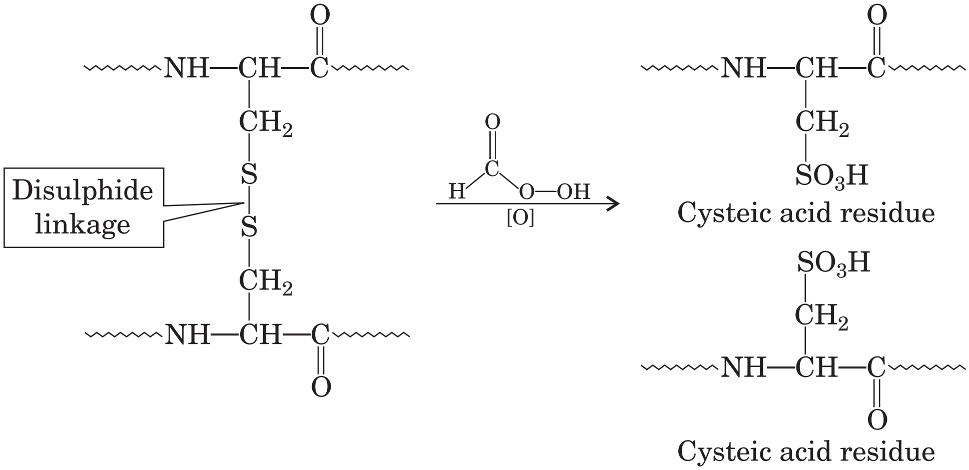
The two cysteine residues may form a disulphide bridge within a single peptide chain, making a ring.

10.2.6 Determination of Structure of Peptides

To determine the structure of a particular peptide, one must know (i) what amino acid residues make up the molecule and how many of each there are, and (ii) the sequence in which they follow one another along the peptide chain.

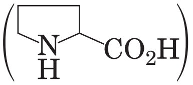
The primary structure (the covalently bonded structure) determination of a peptide involves the steps as follows:

(a) Cleavage of disulphide linkages The first step in determining the primary structure of a peptide is to cleave all the disulphide bonds, separating the individual chains and opening any disulphide-linked rings. A permanent cleavage of such a bond may be carried out with peroxyformic acid because this oxidation converts the disulphide bridges to sulphonic acid (—SO_3H) groups.



(b) Determination of the amino acid composition To analyze the amino acid composition, the peptide chain is completely hydrolyzed by boiling it for 24 hours in 6M HCl (alkali is not used since it causes racemization). The *hydrolysate*, i.e., the resulting mixture of amino acids is placed on the column of an *amino acid analyzer* in which the components of the hydrolysate are dissolved in an aqueous buffer solution and separated by passing them down an ion-exchange column. Ninhydrin is mixed with the solution emerging from the column and the amino acids react with ninhydrin to give purple colour. The absorption of light is recorded on a strip chart as a function of time. The time required for each amino acid to pass through the resin, i.e., its *retention time* depends on how strongly the amino acid interacts with the ion-exchange resin. The amino acids present in the hydrolysate are identified by comparing their retention times with that of the pure amino acids. The relative amounts of amino acids present are determined from the area under each peak which, in fact, proportional to the amount of amino acid producing that peak. From the weight of each amino acid obtained, the number of moles of each amino acid can be calculated and in this way the relative numbers of the various amino acid residues in the peptide can be calculated. At this stage one knows the 'empirical formula' of the peptide. The molecular mass of the peptide is determined by chemical methods and by various physical methods. Then, from the 'empirical formula' and the molecular mass, the 'molecular formula' of the peptide, i.e., the actual number of each kind of amino acid residue present in the peptide molecule is determined.

Example The hydrolysate of the polypeptide *salmine* gives the following results:

Amino acid	**Weight (g/100 g of salmine)**
1. Isolucine [$CH_3CH_2CH(CH_3)CH(NH_2)CO_2H$]	1.28
2. Arginine [$HN{=}C(NH_2){-}NH\ (CH_2)_3CH(NH_2)CO_2H$]	86.40
3. Glycine ($H_2NCH_2CO_2H$)	3.01
4. Alanine [$CH_3CH(NH_2)CO_2H$]	0.89
5. Proline 	6.90
6. Serine [$HOCH_2CH(NH_2)CO_2H$]	7.27
7. Valine [$(CH_3)_2CHCH(NH_2)CO_2H$]	3.68

Therefore, the number of moles of each amino acid in 100 g salmine is as follows:

$$\text{Isoleucine} = \frac{1.28\ \text{g}}{131\ \text{g/mole}} = 0.01\ \text{mole}$$

$$\text{Arginine} = \frac{86.40\ \text{g}}{174\ \text{g/mole}} = 0.50\ \text{mole}$$

$$\text{Glycine} = \frac{3.01\ \text{g}}{75\ \text{g/mole}} = 0.04\ \text{mole}$$

$$\text{Alanine} = \frac{0.89\ \text{g}}{89\ \text{g/mole}} = 0.01\ \text{mole}$$

$$\text{Proline} = \frac{6.90\ \text{g}}{131\ \text{g/mole}} = 0.06\ \text{mole}$$

$$\text{Serine} = \frac{7.29\ \text{g}}{105\ \text{g/mole}} = 0.07\ \text{mole}$$

$$\text{Valine} = \frac{3.68\ \text{g}}{117\ \text{g/mole}} = 0.03\ \text{mole}$$

Hence, the empirical formula of the polypeptide salmine is:

$$\text{Ala Arg}_{50}\ \text{Gly}_4\ \text{Ile Pro}_6\ \text{Ser}_7\ \text{Val}_3$$

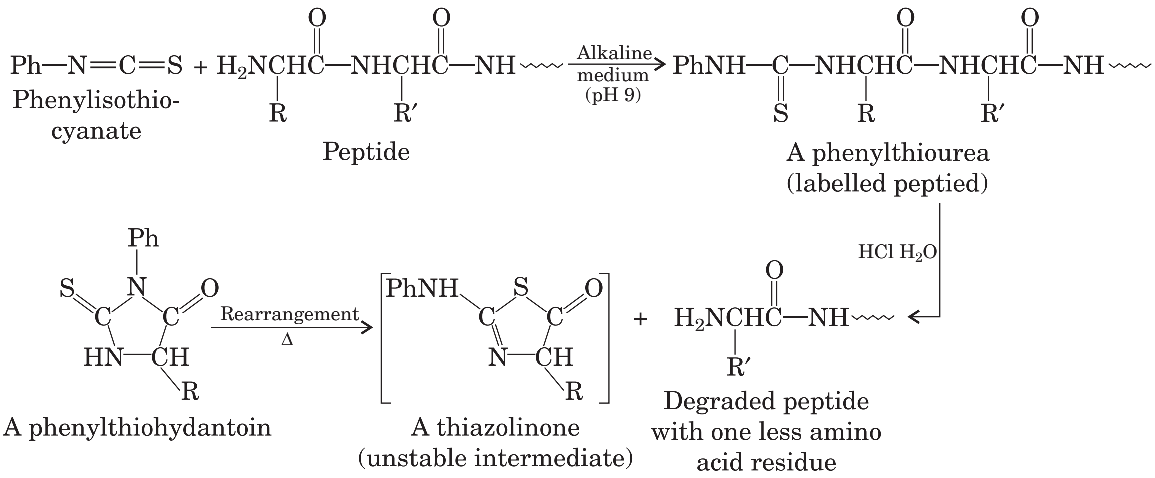
The molecular mass of salmine is about 10,000. Since there is 0.01 mole Ile in 100 g of salmine, there must be 1 mole Ile in 10,000 g of salmine. This means that there is only one Ile per molecule, and the molecular formula is the same as the empirical formula.

(c) Determination of the sequence of amino acids This is accomplished by using the technique of *terminal residue analysis* or *end group analysis* coupled with partial hydrolysis.

Terminal residue analysis The amino acid analyzer determines the amino acids present in a peptide molecule, but it is unable to indicate their sequence, i.e., the order in which they are linked together. The N-terminal residue (which contains a free *alpha*-amino group) and the C-terminal residue (which contains a free carboxyl group *alpha* to a peptide linkage) in a peptide chain are identified by using some specific reagents. The peptide is treated with a reagent which reacts with a particular terminus to form a *tagged* peptide. This is subject to partial hydrolysis that releases the tagged amino acid which is identified. The process is repeated on the rest of the chain and the result gives an idea of the amino acid sequence. This general method of peptide sequencing is called *terminal residue analysis*.

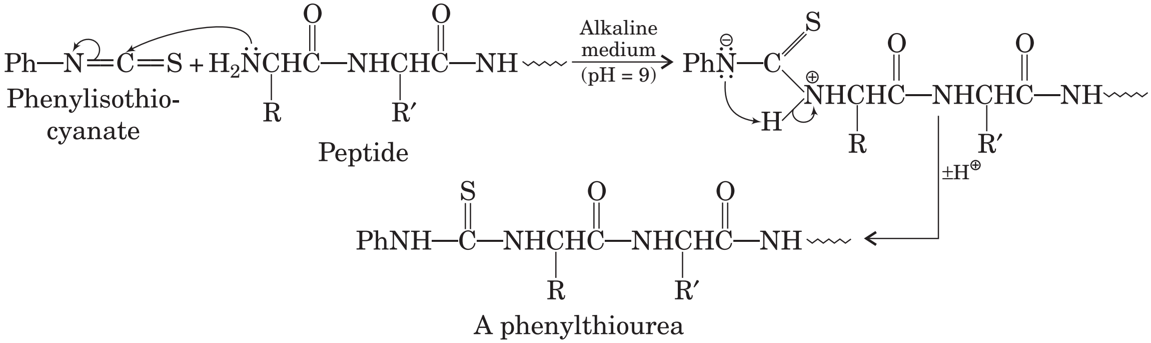
N-Terminal residue analysis The methods generally used for sequencing peptides from the N terminus are as follows:

(a) The Edman degradation This is the most effective and frequently used method for determining the N-terminal amino acid residue. In this method, the peptide is allowed to react with phenylisothiocyanate. Nucleophilic addition by the N-terminal amino group to the reagent produces a phenylthiourea derivative of the peptide. Mild hydrolysis with hydrochloric acid selectively removes the N-terminal residue as a thiozolinone derivative from the remainder of the peptide. This derivative (unstable under the conditions of the reaction) rearranges to a phenylthiohydantoin (PTH), which is isolated and identified by comparing it with standard samples of PTH derivatives of known amino acids. This gives the identity of the original N-terminal amino acid. The beauty of the Edman degradation is that it allows identification of the N-terminal residue while leaving the remaining part of the peptide intact. Further Edman degradations are used to identify additional amino acids in the chain. The process is well suited to automation and several types of automated amino-acid sequencers have been developed for this procedure.

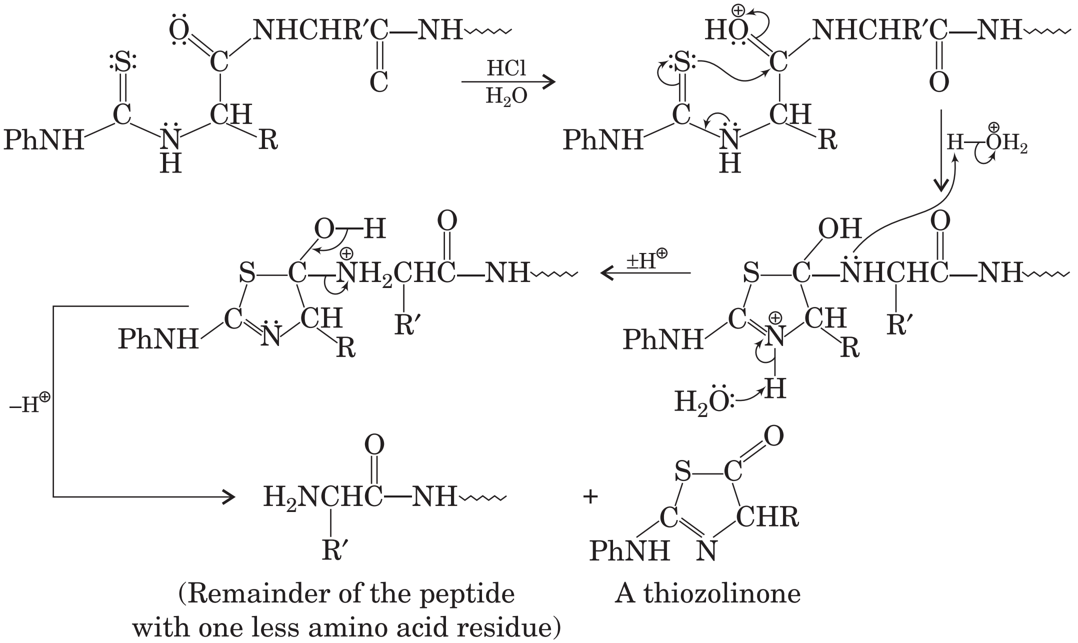


Mechanism The mechanisms for the steps involved in the Edman degradation may be outlined as follows:

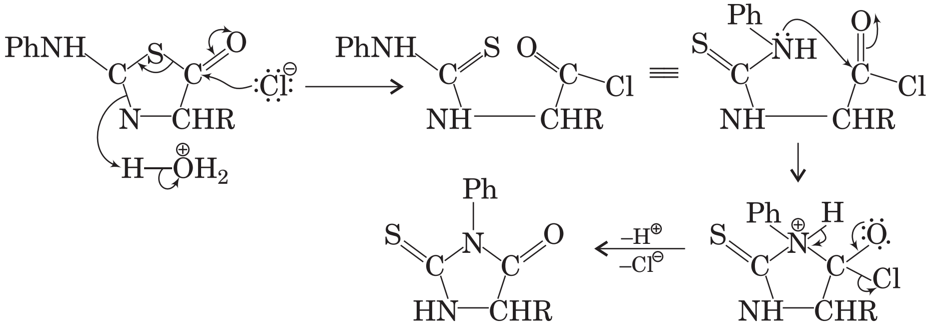
Step 1 Phenyliosothiocyanate undergoes nucleophilic attack by the peptide to yield a phenylthiourea.



Step 2 The thiourea is cleaved in aqueous acid without breaking the other amide bonds in the peptide. Sulphur is an excellent neighbouring group, and the introduction of the thiourea places a sulphur atom in just the right position to aid in cleavage of the N-terminal residue from the rest of the peptide. The process involves initial protonation of the amino terminus carbonyl group. The neighbouring sulphur then adds to the carbonyl carbon, triggering the cleavage reaction to yield a molecule of thiazolinone.

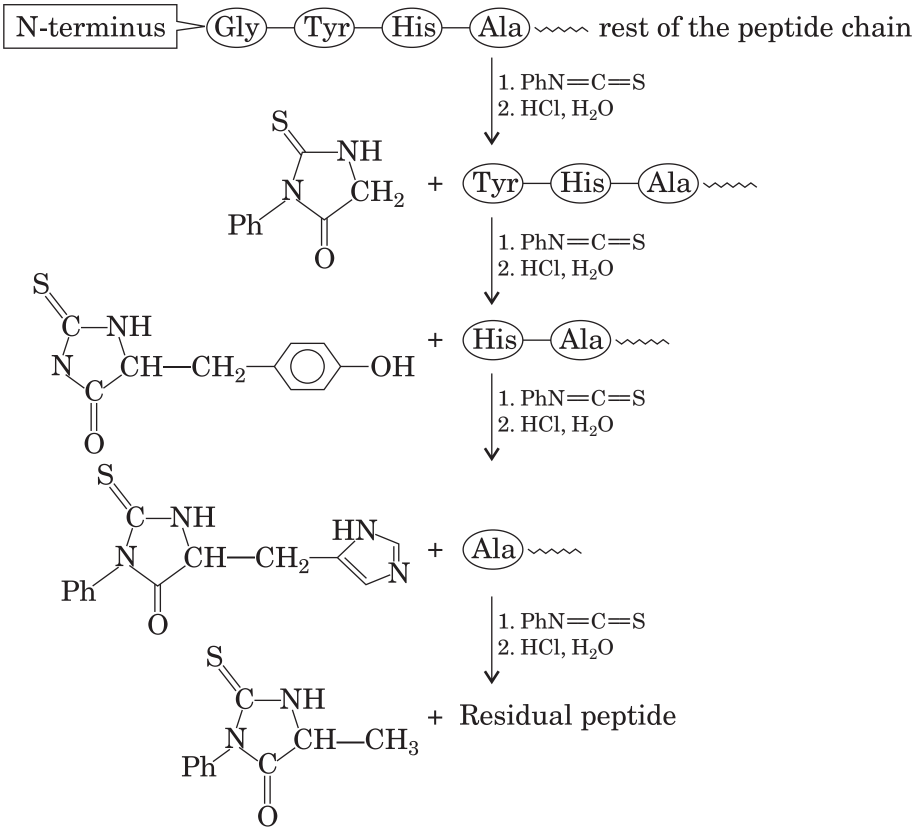


Step 3 The less stable thiazolinone intermediate isomerizes to a more stable phenylthiohydantoin derivative under the reaction conditions.

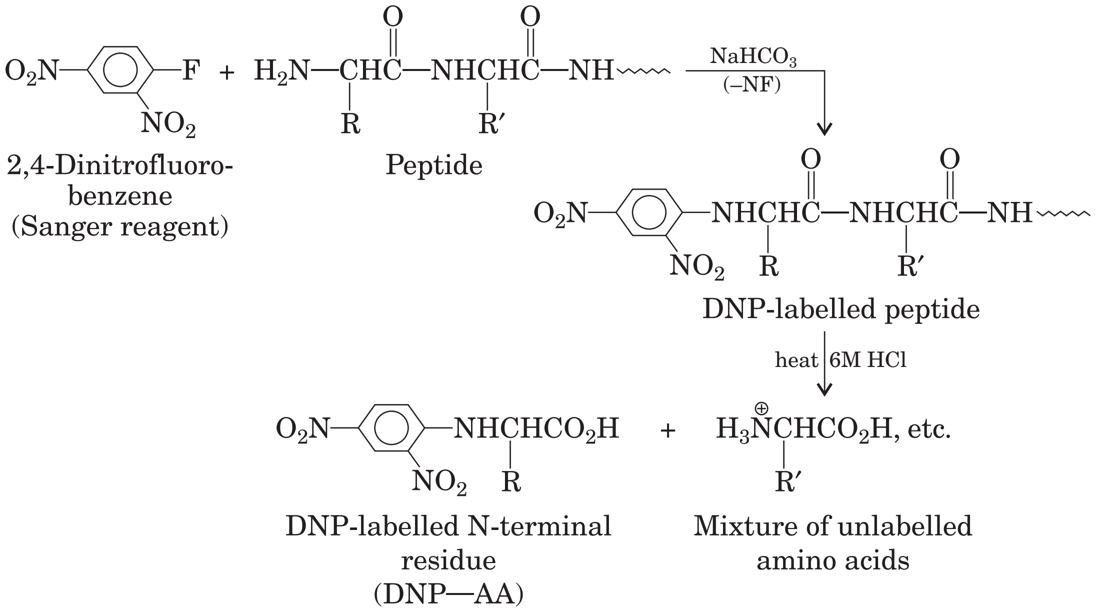


A phenylthiohydantoin

Example The result of a series of Edman degradation on an N-terminal Gly-Tyr-His-Ala-peptide may be outlined as follows:



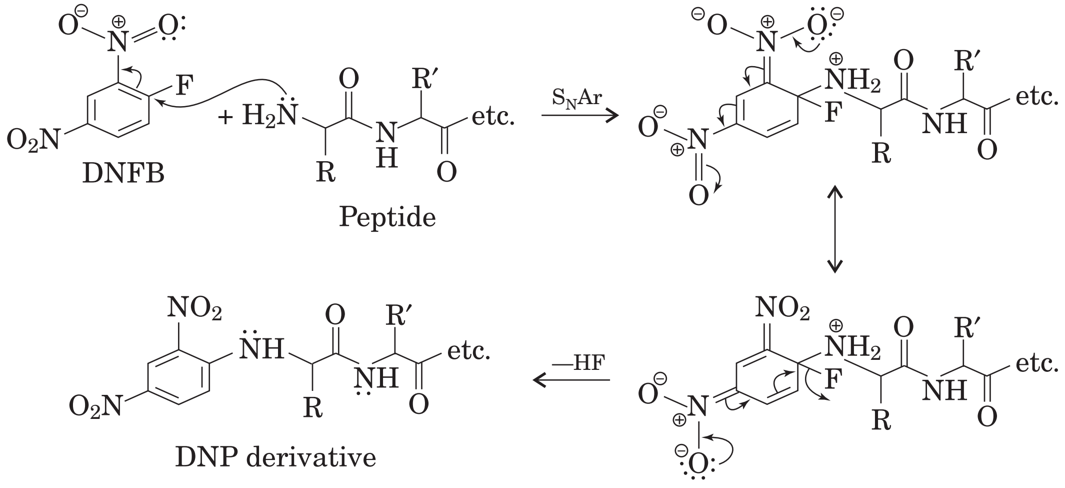
(b) Sanger method Frederick Sanger introduced this procedure in 1945. In this method, peptide is treated with the **Sanger reagent**, 2,4-dinitrofluorobenzene (DNFB) in mildly basic solution. Due to presence of strong electron-attracting nitro groups at the appropriate positions, the reagent undergoes a facile nucleophilic aromatic substitution reaction (S_NAr) involving the free amino group of the N-terminal residue to give a peptide in which the N-terminus is labelled with a 2,4-dinitrophenyl group. The labelled peptide is then hydrolyzed with aqueous HCl to the component amino acid residues, and the N-terminal residue, labelled by the 2,4-dinitrophenyl group, is separated. The labelled amino acid is then identified by comparing its chromatographic behaviour with that of standard samples of 2,4-dinitrophenyl-labelled amino acids.



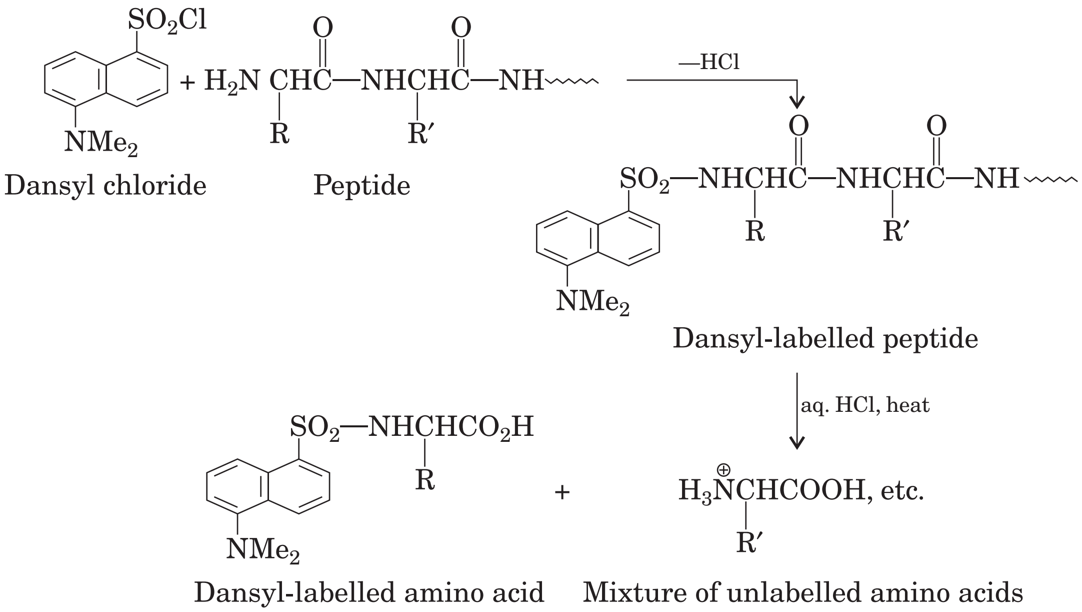
Due to presence of an electron-attracting 2,4-dinitrophenyl group, the labelled amino acid is relatively nonbasic and is, therefore, insoluble in dilute aqueous acid. The other amino acids (not labelled) dissolve in dilute aqueous acid. Thus the electron-withdrawing property of the 2,4-DNP group makes separation of the labelled amino acid very easy.

One drawback of this method is that the hydrolytic cleavage leads to complete breakdown of the peptide to the component amino acids and therefore, the sequence of amino acids cannot be easily determined.

Mechanism The base abstracts a proton from the terminal $—\overset{\oplus}{N}H_3$ group to give a free amino function. The nucleophilic $—NH_2$ group then displaces fluoride from DNFB and yields a peptide in which the N-terminal amino acid is labelled with 2,4-dinitrophenyl (DNP) group. The mechanism of the reaction may be outlined as follows:



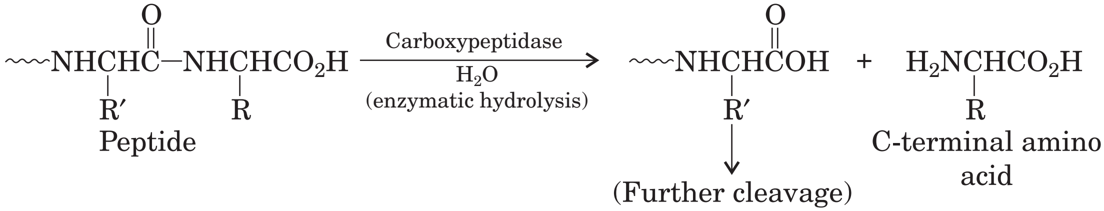
(c) The method involving dansylation In this method, the peptide is allowed to react with 5-(dimethylamino)naphthalene-1-sulfinyl chloride (dansyl chloride). The reagent labels the N-terminal amino acid as a sulfonamide derivative (the process is called *dansylation*). The labelled peptide is then hydrolyzed in aqueous acid to yield its constituent amino acids along with the densyl derivative of the N-terminal amino acid, which is isolated and identified (sulfonamides are not hydrolyzed by aqueous acid) spectroscopically in microgram amounts.



In this case also, the hydrolytic cleavage brings about the complete breakdown of the peptide to the component amino acids and, therefore, the amino acid sequence cannot be easily determined.

C-Terminal residue analysis:

(a) Enzymatic method One successful method of determining the C-terminal residue has been enzymatic rather than chemical. The enzyme *carboxypeptidase A* (obtained from the pancreas) catalyzes only the hydrolysis of the C-terminal peptide bond. When the peptide is incubated with *carboxy-peptidase A*, the first amino acid to appear in solution is the one that occupies the C-terminal position. Once the C-terminal amino acid has been cleaved, this enzyme catalyzes the hydrolysis of the peptide bond to the new C-terminal amino acid. Eventually, the entire peptide is hydrolyzed to the constituent amino acids. The concentration of free amino acid is monitored as a function of time. The order of their decreasing concentration indicates the position of each amino acid residue with respect to the C-terminus of the original peptide.

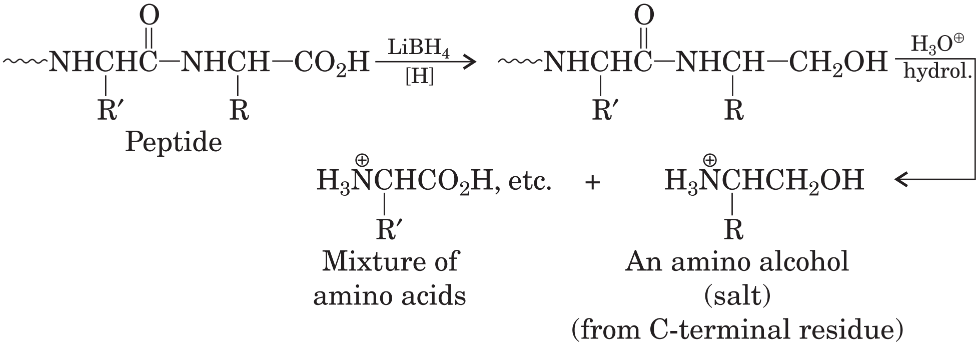


$$\sim\!\sim\!\sim\text{NH}\underset{\substack{|\\R'}}{\text{C}}\text{H}\overset{\substack{O\\\|}}{\text{C}}-\text{NH}\underset{\substack{|\\R}}{\text{C}}\text{HCO}_2\text{H} \xrightarrow[\substack{H_2O\\(\text{enzymatic hydrolysis})}]{\text{Carboxypeptidase}} \sim\!\sim\!\sim\text{NH}\underset{\substack{|\\R'\\\downarrow\\(\text{Further cleavage})}}{\text{C}}\text{H}\overset{\substack{O\\\|}}{\text{C}}\text{OH} + \text{H}_2\text{N}\underset{\substack{|\\R}}{\text{C}}\text{HCO}_2\text{H}$$

Peptide

C-terminal amino acid

(b) Chemical methods **(i) Treatment of the peptide with lithium borohydride followed by acidic hydrolysis and analyses:** $LiBH_4$ reduces the terminal —CO_2H group to a —CH_2OH group. The resulting compound upon hydrolysis by aqueous acid yields a mixture of an amino alcohol and other amino acid residues. The amino alcohol is identified and in this way the C-terminal residue is identified.



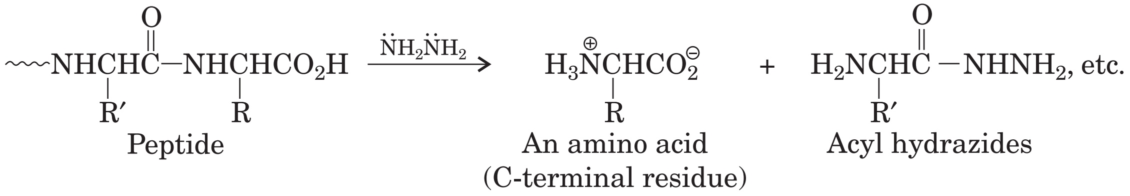
$$\sim\!\sim\!\sim\text{NH}\underset{\substack{|\\R'}}{\text{C}}\text{H}\overset{\substack{O\\\|}}{\text{C}}-\text{NH}\underset{\substack{|\\R}}{\text{C}}\text{H}-\text{CO}_2\text{H} \xrightarrow[\text{[H]}]{\text{LiBH}_4} \sim\!\sim\!\sim\text{NH}\underset{\substack{|\\R'}}{\text{C}}\text{H}\overset{\substack{O\\\|}}{\text{C}}-\text{NH}\underset{\substack{|\\R}}{\text{C}}\text{H}-\text{CH}_2\text{OH} \xrightarrow[\text{hydrol.}]{\text{H}_3\text{O}^{\oplus}} \text{H}_3\overset{\oplus}{\text{N}}\underset{\substack{|\\R'}}{\text{C}}\text{HCO}_2\text{H}, \text{etc.} + \text{H}_3\overset{\oplus}{\text{N}}\underset{\substack{|\\R}}{\text{C}}\text{HCH}_2\text{OH}$$

Peptide

Mixture of amino acids

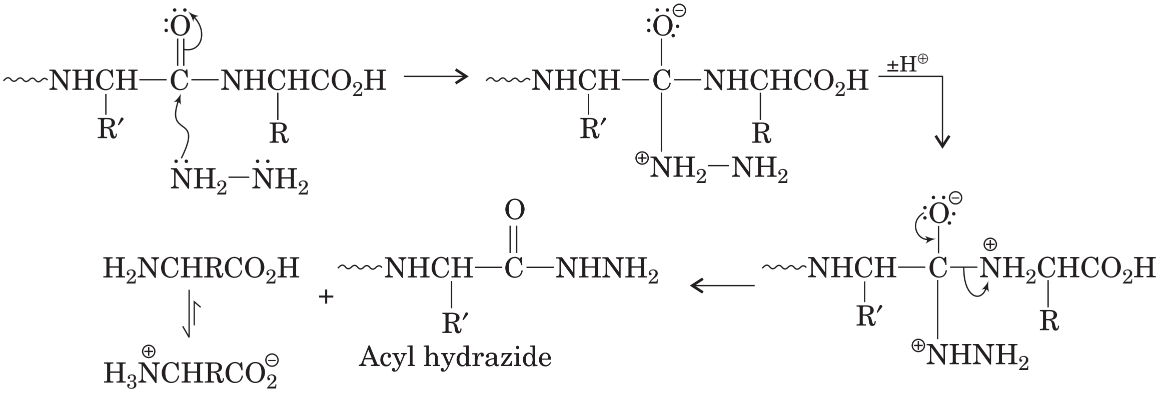
An amino alcohol (salt) (from C-terminal residue)

(ii) Treatment of the peptide with hydrazine followed by analysis of the products (Akabori method) Hydrazine (NH_2NH_2) is a good nucleophile. When it is treated with peptide, it cleaves the amide linkage to yield acyl hydrazides. The C-terminal residue remains unaffected. It is isolated and then identified.



$$\sim\sim\sim NH\underset{R'}{C}H\overset{O}{\overset{\|}{C}}-NH\underset{R}{C}HCO_2H \xrightarrow{\ddot{N}H_2\ddot{N}H_2} H_3\overset{\oplus}{N}\underset{R}{C}HCO_2^{\ominus} + H_2N\underset{R'}{C}H\overset{O}{\overset{\|}{C}}-NHNH_2, \text{ etc.}$$

Mechanism:



Partial hydrolysis (breaking the peptide into shorter chains) Sequential analysis involving the Edman degradation or the enzyme *carboxypeptidase* becomes impractical with peptides of appreciable size. In that case, the peptide is cleaved into smaller chains by partial hydrolysis, and the shortened chains formed—dipeptide, tripeptide, and so on — are then sequenced, with the aid of terminal residue analysis. The sequence of the original peptide is then determined by fitting the short chains, looking for points of overlap.

Partial hydrolysis can be accomplished either by using dilute acid with a short reaction time or by using enzymes such as *trypsin* and *chymotrypsin*. The acid-catalyzed cleavage is not much selective because it leads to a mixture of short fragments resulting from cleavage at various positions. Enzymes, on the other hand, are more selective, giving cleavage at predictable points in the chain. Trypsin cleaves the chain at the carboxyl groups of the basic amino acids **lysine** and **arginine**, whereas chymotrypsin cleaves the chain at the carboxyl groups of the aromatic amino acids **phenylalanine**, **tyrosine** and **tryptophan**.

Let's consider a pentapeptide as an example to illustrate the use of partial hydrolysis. The pentapeptide is known to contain aspartic acid, glutamic acid, histidine, phenylalanine, and valine. With this information, the 'molecular formula' of the pentapeptide can be written as follows (commas indicate unknown sequence):

Asp, Glu, His, Phe, Val

Let us assume that using Sanger reagent and *carboxypeptidase*, phenylalanine and histidine are found to be N-terminal and C-terminal residues respectively. So far we know the following:

Phe (Asp, Glu, Val) His

Acid-catalyzed partial hydrolysis of this pentapeptide gives a mixture of four dipeptides (along with individual amino acids and larger pieces). These are as follows:

Phe – Val + Val – Asp + Asp – Glu + Glu – His

The points of overlap of the dipeptides (i.e., Val, Asp, and Glu) tell us that the complete structure of the pentapeptide is as follows:

Phe – Val – Asp – Glu – His

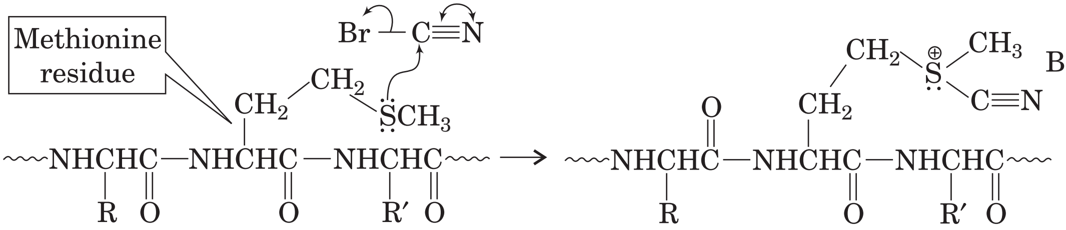
[The complete sequence can also be determined by matching the overlapping regions as follows:

Phe – Val
Val – Asp
Asp – Glu
Glu – His

Phe – Val – Asp – Glu – His]

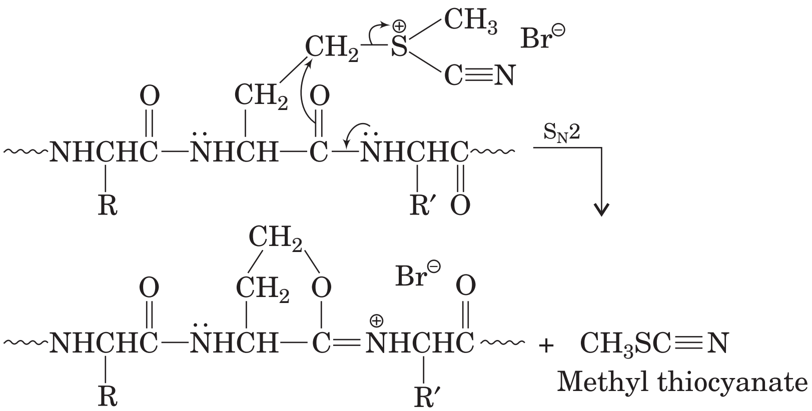
Use of cyanogen bromide (BrCN) in selective cleavage of a peptide When a peptide is treated with cyanogen bromide (Br—C≡N) in aqueous HCl, a peptide bond is cleaved specifically at the carboxyl end of each methionine. The cleavage of the peptide that proceeds through the steps as follows:

Step 1 The sulphur atom (a good nucleophile) in the methionine side chain displaces bromide from cyanogen bromide to yield a sulphonium ion.

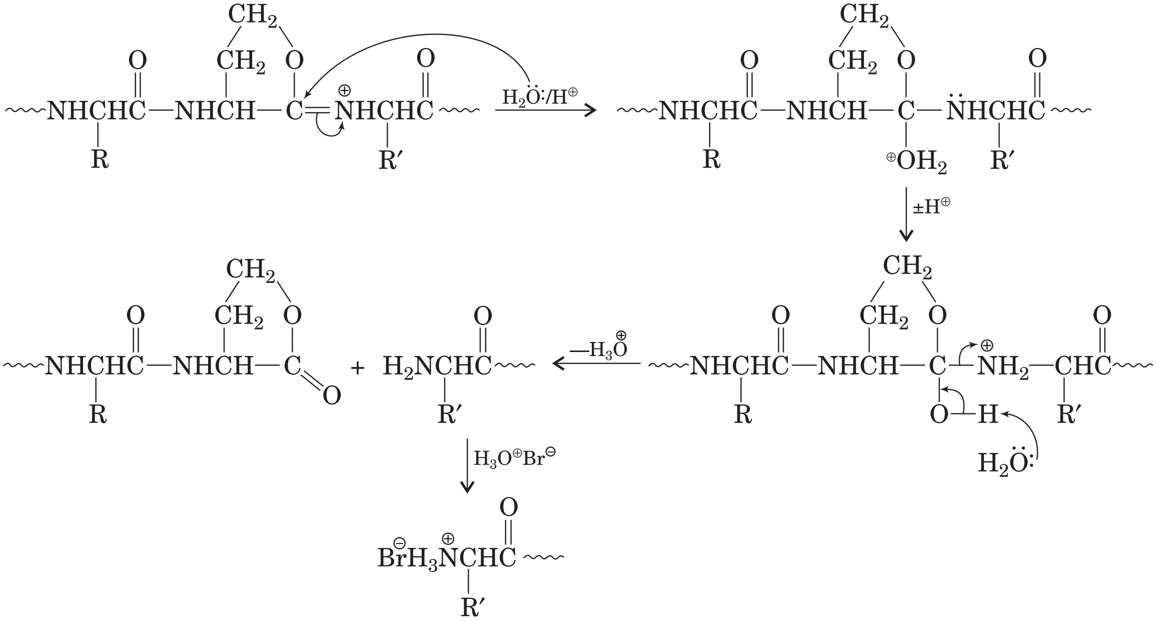


A peptide A sulphonium ion

Step 2 The sulphonium ion, with its electron-attracting —CN group, is an excellent leaving group. Because of this, it is displaced readily (S_N2) by the carbonyl oxygen of the neighbouring amide bond to form a five-membered ring.



Step 3 The resulting salt undergoes acid-catalyzed hydrolysis to form a lactone. Cleavage of the peptide bond actually takes place in this step.



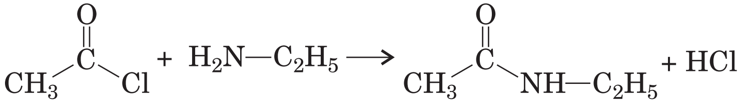
10.2.7 Peptide Synthesis

Total synthesis of peptides is rarely found to be an economically viable method for their commercial production. Important peptides are usually derived from biological sources. Recombinant DNA techniques are improving the quality and availability of pharmaceutical peptides. Laboratory synthesis of peptides is still an important area of drug development. One of the most prominent peptide drug is insulin. The insulin required for the treatment of diabetes used to be obtained by extraction from the pancreas glands of cows and pigs. Since the early 1980s, this natural insulin has been replaced by the insulin prepared by the recombinant DNA technology. This insulin is not only identical to human insulin, it is both safer and less expensive than insulin obtained from animals. Other than the biological methods typified by the synthesis of insulin, there are two major approaches to peptide synthesis: (i) solution-phase method and (ii) solid-phase method. Although the two procedures differ in respect to the phase in which the synthesis is carried out, the overall strategy is the same in both.

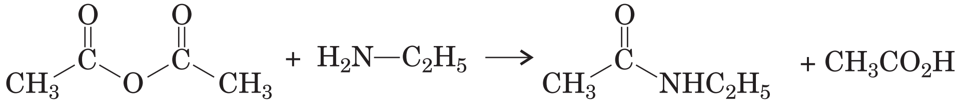
10.2.7.1 Solution-phase Peptide Synthesis

Peptide synthesis requires the formation of amide linkage between the proper amino acids in the proper sequence. With simple acids and amines, we would make an amide linkage simply by converting the acid to an activated derivative like acyl halide or anhydride followed by allowing it to react with an amine. For example:

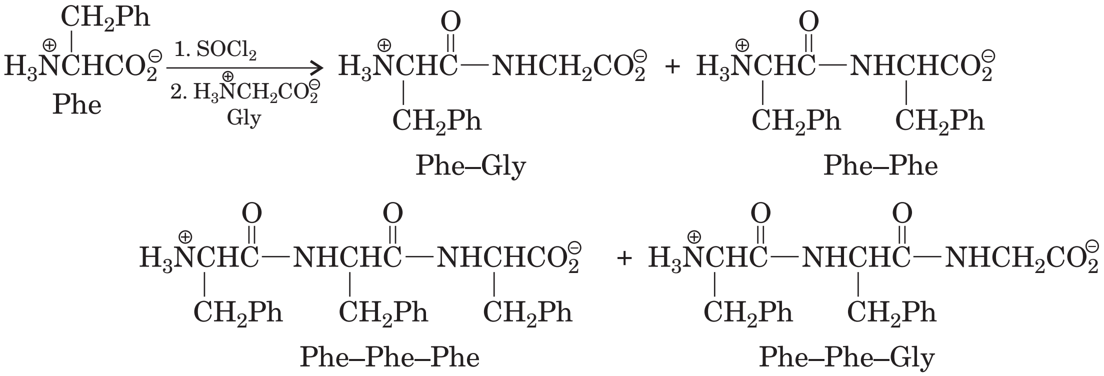
(i)



(ii)



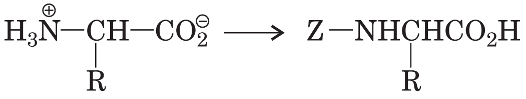
Amide formation, however, becomes very complicated when both the carboxyl group and the amino group are present in the same molecule, as they are in an amino acid and especially, when we are going to synthesize a peptide where the sequence of different amino acid residues is all-important. For example, let us consider the synthesis of the simple dipeptide Phe-Gly. The carboxyl group of phenylalanine is first activated by converting it to an acid chloride or anhydride, and then it is allowed to react with glycine. Unfortunately, however, phenylalanyl chloride cannot be prevented from reacting with itself. So, the reaction would yield not only Phe–Gly but also Phe–Phe. It could also lead to Phe–Phe–Phe and Phe–Phe–Gly, and so on. The yield of the desired product would be low, and it would be very difficult to separate the dipeptide, the tripeptide, and so on. This is the basic problem of peptide synthesis.



The problem can be solved by protecting the amino group of the first amino acid before activating it and then allowing it to react with the second. By protecting the amino group it means that the reactivity of the amino group is to be suppressed by converting it to some other group of low nucleophilicity—one that will not react with a reactive acyl derivative. There are many such protecting groups. However, the group that can be removed later (after synthesizing the amide linkage) without breaking any of the peptide bonds in the product must be chosen.

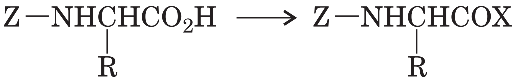
Solution phase peptide synthesis begins at the N-terminus and ends at the C-terminus, or left to right as we draw the peptide. The steps involved in the synthesis of a dipeptide ($H_3\overset{\oplus}{N}CHRCONHCHR'CO_2^{\ominus}$) are as follows:

(i) **Protection of the amino group:** The amino group of the N-terminal amino acid is to be blocked first in order to make it unreactive (very weak as a nucleophile):



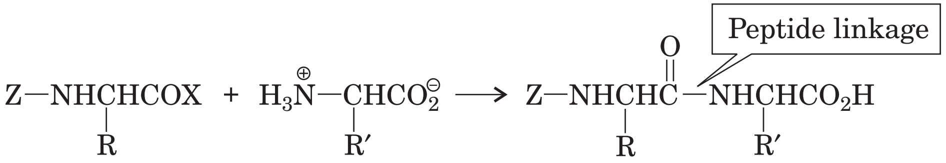
$$H_3\overset{\oplus}{N}-\underset{R}{\underset{|}{C}}H-CO_2^{\ominus} \longrightarrow Z-NH\underset{R}{\underset{|}{C}}HCO_2H$$

(ii) **Activation of the carboxyl group:** The carboxyl group of the N-protected amino acid is to be activated in order to make it more reactive than the carboxyl group of the C-terminal amino acid residue.



$$Z-NH\underset{R}{\underset{|}{C}}HCO_2H \longrightarrow Z-NH\underset{R}{\underset{|}{C}}HCOX$$

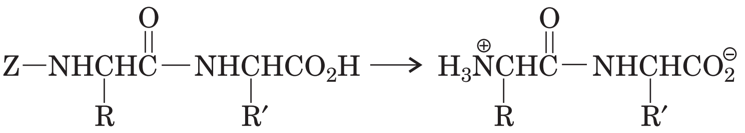
(iii) **Formation of the peptide linkage:** The N-terminal amino acid with the protected amino group and activated carboxyl group is to be treated with the C-terminal amino acid in a basic medium.



$$Z-NH\underset{R}{\underset{|}{C}}HCOX + H_3\overset{\oplus}{N}-\underset{R'}{\underset{|}{C}}HCO_2^{\ominus} \longrightarrow Z-NH\underset{R}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}-NH\underset{R'}{\underset{|}{C}}HCO_2H$$

Peptide linkage

(iv) **Removal of the protecting group:** The protected amino group of the N-terminal residue is to be deprotected under mild condition in which the peptide linkage remains intact.

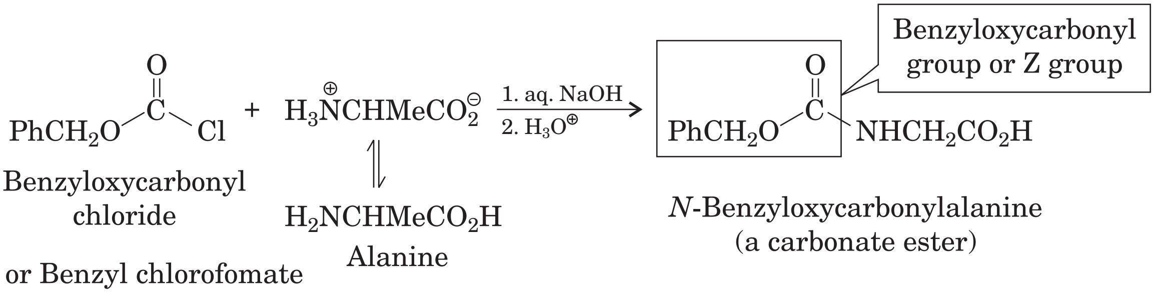


$$Z-NH\underset{R}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}-NH\underset{R'}{\underset{|}{C}}HCO_2H \longrightarrow H_3\overset{\oplus}{N}\underset{R}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}-NH\underset{R'}{\underset{|}{C}}HCO_2^{\ominus}$$

A dipeptide

Protection and deprotection of the amino group The amino group is most often protected by acylation. The amino-protecting groups, the corresponding reagents, and their removal procedures are discussed below with the mechanisms of the reactions involved:

(i) The benzyloxycarbonyl group ($PhCH_2O—\overset{\overset{O}{\|}}{C}—$) or simply the Z group (abbreviated form) is one of the frequently used amino-protecting groups. It is attached by acylation of an amino acid with benzyloxycarbonyl chloride or benzyl chloroformate. For example, the amino group of alanine can be protected as follows:

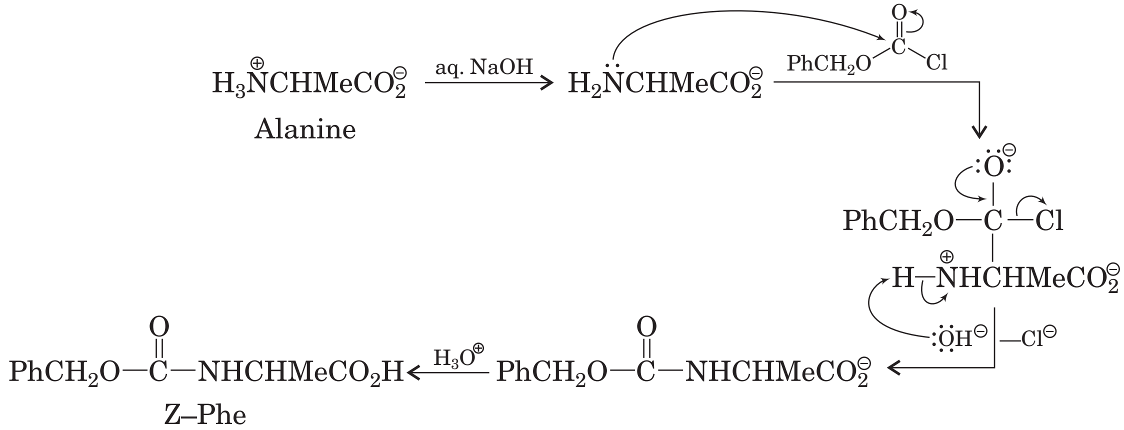


Benzyloxycarbonyl chloride or Benzyl chlorofomate

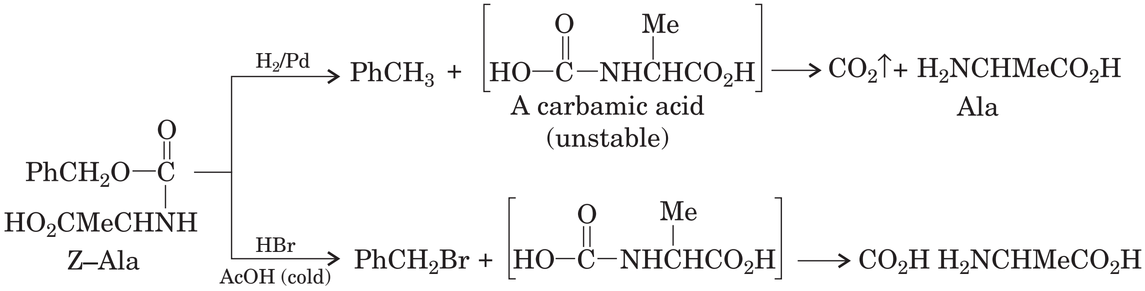
$H_2NCHMeCO_2H$ Alanine

N-Benzyloxycarbonylalanine (a carbonate ester)

Mechanism:

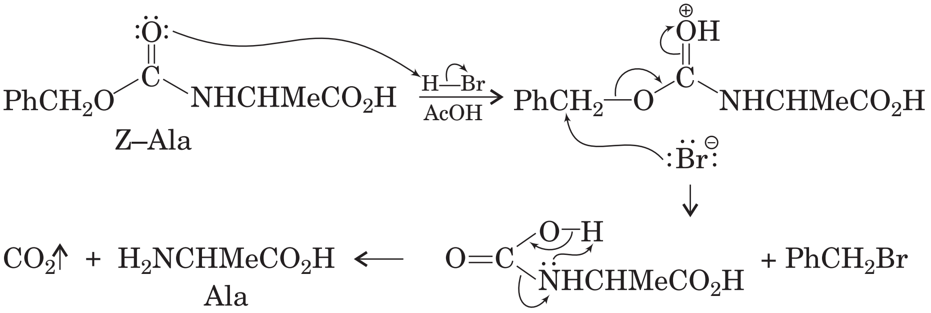


*** Removal of the Z group** The benzyloxycarbonyl group or Z group can be removed by catalytic hydrogenation or by treating the compound with cold HBr in acetic acid.

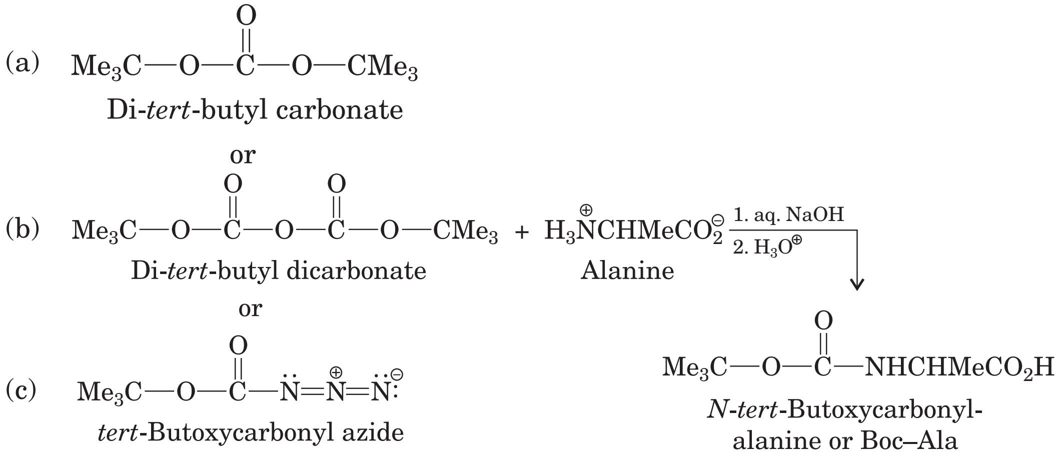


[The benzyloxycarbonyl group is also called the carbobenzoxy group (abbreviated Cbz).]

Mechanism:



(ii) A similar N-terminal-protecting group is *tert*-butoxycarbonyl group ($\mathrm{Me_3CO\overset{|}{C}{=}O}$) or simply the Boc group (abbreviated Boc). It is attached by acylation of an amino acid with di-*tert*-butyl carbonate or di-*tert*-butyl dicarbonate or *tert*-butoxycarbonyl azide. For example, the amino group of alanine can be protected as follows:



(a) $\mathrm{Me_3C{-}O{-}\overset{O}{\overset{\|}{C}}{-}O{-}CMe_3}$

Di-*tert*-butyl carbonate

or

(b) $\mathrm{Me_3C{-}O{-}\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}{-}O{-}CMe_3} + \mathrm{H_3\overset{\oplus}{N}CHMeCO_2^{\ominus}} \xrightarrow[2.\ \mathrm{H_3O^{\oplus}}]{1.\ \text{aq. NaOH}}$

Di-*tert*-butyl dicarbonate Alanine

or

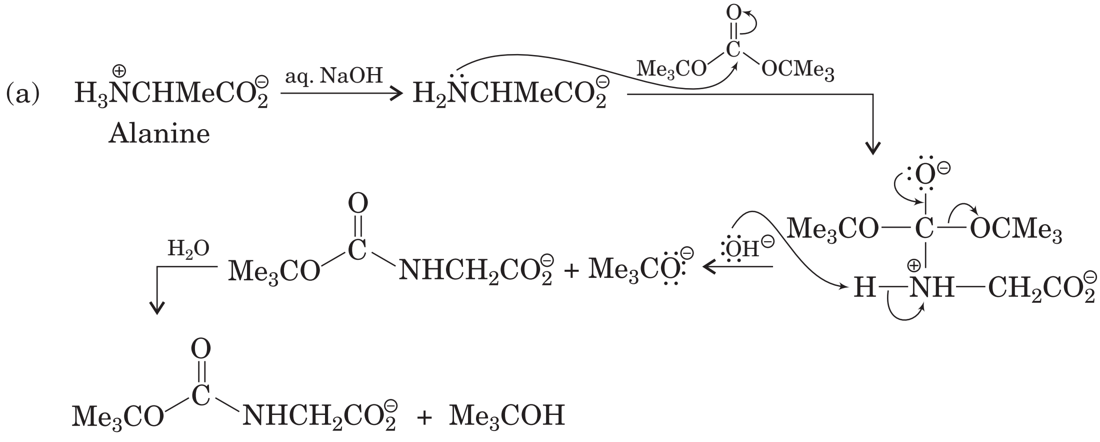
(c) $\mathrm{Me_3C{-}O{-}\overset{O}{\overset{\|}{C}}{-}\ddot{N}{=}\overset{\oplus}{N}{=}\ddot{N}^{\ominus}}$

tert-Butoxycarbonyl azide

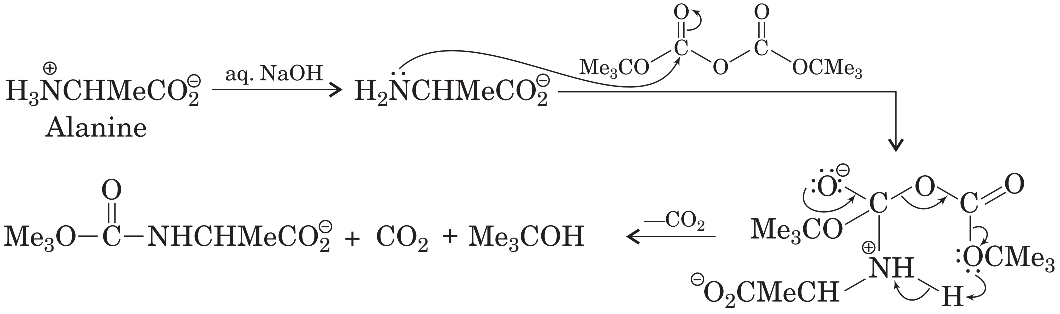
$\mathrm{Me_3C{-}O{-}\overset{O}{\overset{\|}{C}}{-}NHCHMeCO_2H}$

N-*tert*-Butoxycarbonyl-alanine or Boc–Ala (a carbamate ester)

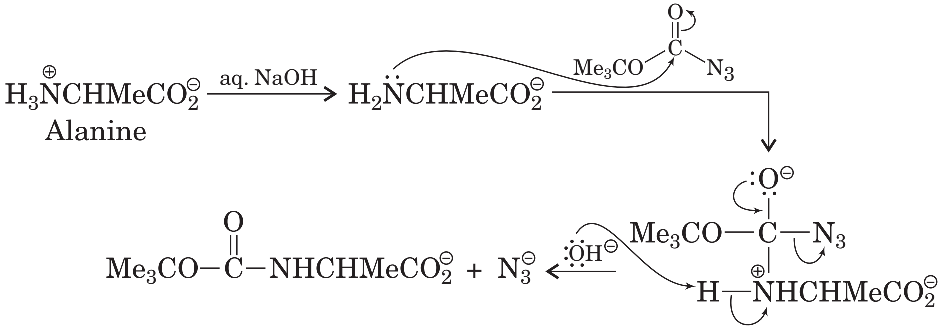
Mechanism:



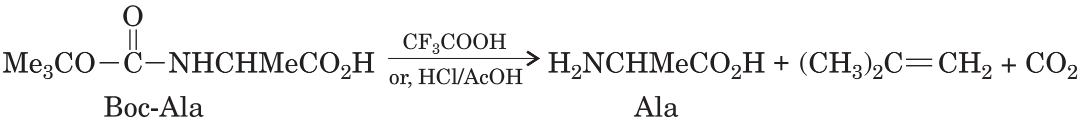
(b)



(c)

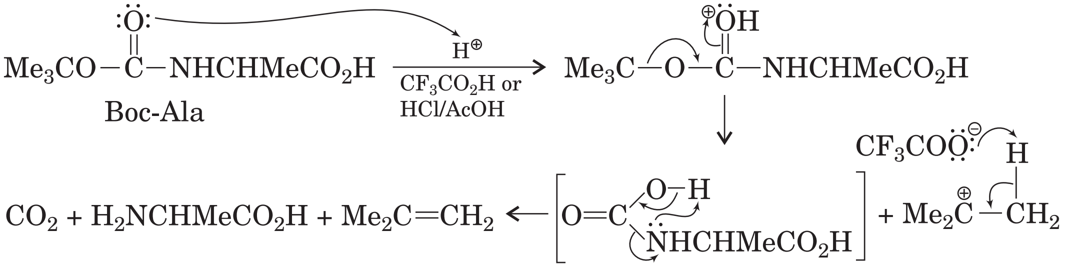


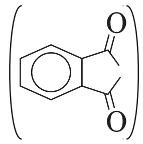
*** Removal of Boc group** The *tert*-butoxycarbonyl group or Boc group can be removed through treatment with anhydrous acid, such as trifluoroacetic acid (CF_3CO_2H) or hydrogen chloride in acetic acid.



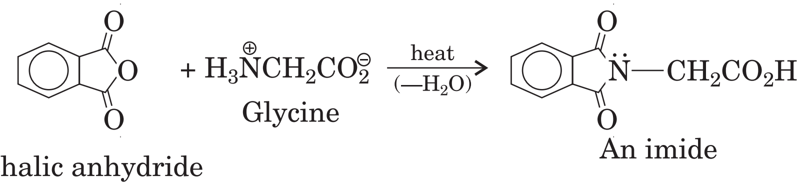
$$\underset{\text{Boc-Ala}}{Me_3CO-\overset{\overset{\displaystyle O}{\|}}{C}-NHCHMeCO_2H} \xrightarrow[\text{or, HCl/AcOH}]{CF_3COOH} \underset{\text{Ala}}{H_2NCHMeCO_2H} + (CH_3)_2C{=}CH_2 + CO_2$$

Mechanism:

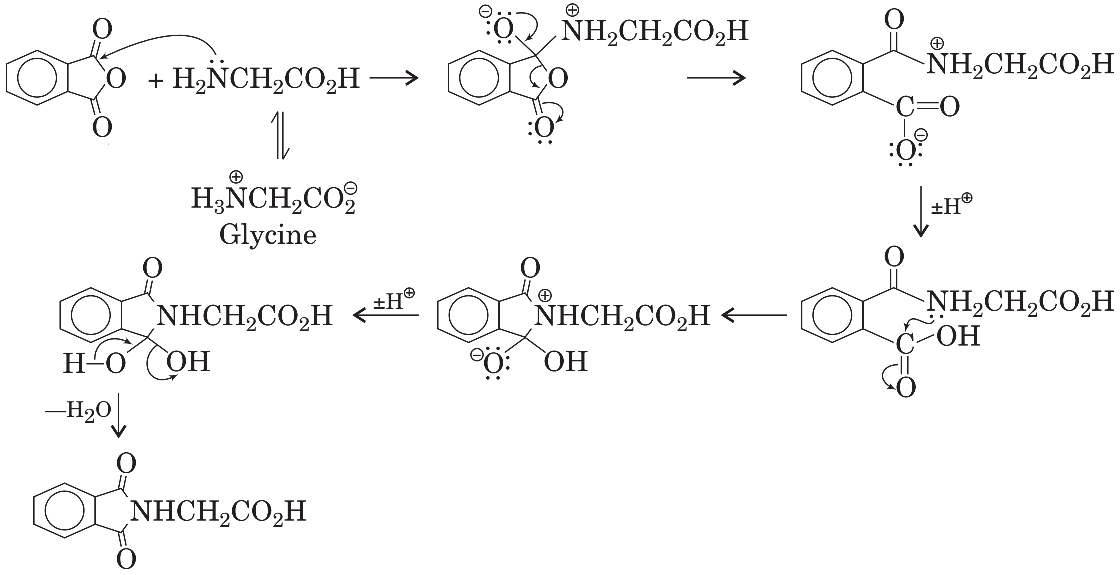


(iii) The phthaloyl group  can be used to protect the amino group. The protection may be carried out by heating an amino acid with phthalic anhydride.

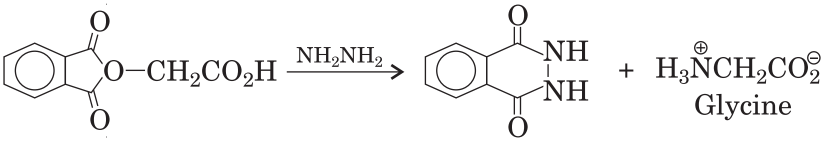
For example:



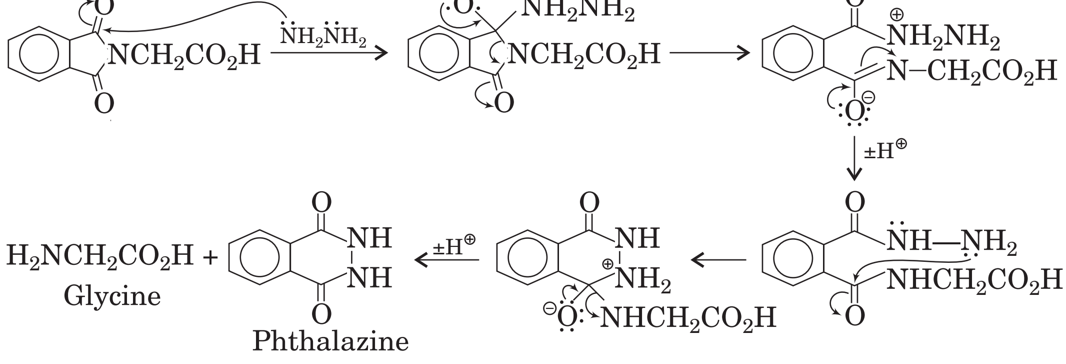
Mechanism:


+ $H_2\ddot{N}CH_2CO_2H$
$H_3\overset{\oplus}{N}CH_2CO_2^{\ominus}$
Glycine
$\overset{\oplus}{N}H_2CH_2CO_2H$
$\overset{\oplus}{N}H_2CH_2CO_2H$
C=O
±$H^{\oplus}$
$NH_2CH_2CO_2H$
OH
$\overset{\oplus}{N}HCH_2CO_2H$
OH
±$H^{\oplus}$
$NHCH_2CO_2H$
H–O
OH
—H_2O
$NHCH_2CO_2H$

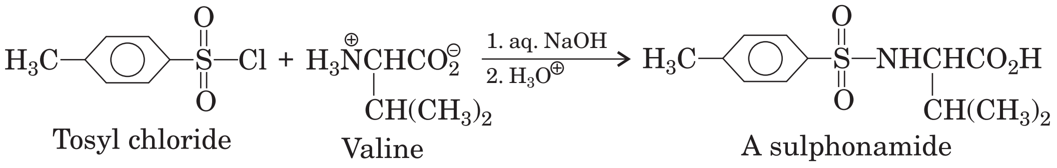
*** Removal of the phthaloyl group** The phthaloyl group can be removed by treating the imide with hydrazine.



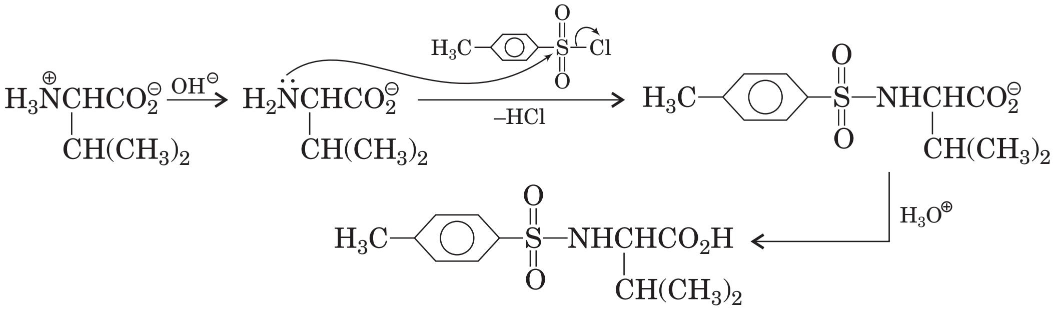
Mechanism:



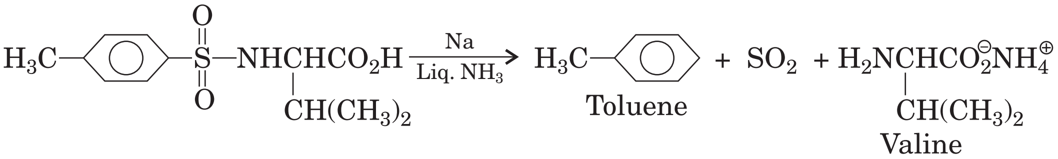
(iv) The tosyl group (—OTs) can be used as an amino-protecting group. Protection by this group may be carried out by allowing the amino acid with tosyl chloride (*p*-toluenesulphonyl chloride). For example:



Mechanism:



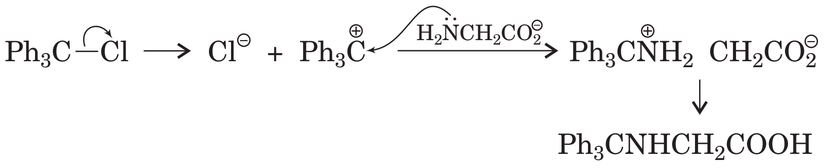
*** Removal of the tosyl group** The tosyl group can be removed by reducing with metallic sodium in liquid ammonia.



(v) The triphenylmethyl group or trityl group (Ph_3C—) can be used as an amino protecting group and this can be introduced by allowing the amino acid to react with triphenylmethyl chloride or trityl chloride in the presence of a base. For example:

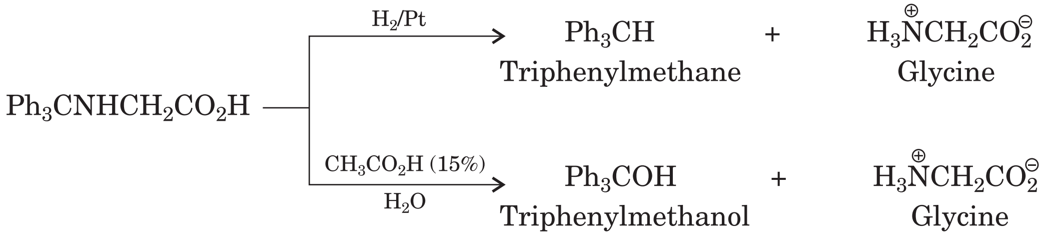
$$\underset{\substack{\text{Triplenylmethyl chloride}\\ \text{or}\\ \text{Trityl chloride}}}{Ph_3CCl} + \underset{\text{Glycine}}{H_3\overset{\oplus}{N}CH_2CO_2^{\ominus}} \xrightarrow{Et_3N} Ph_3CNHCH_2CO_2H$$

Mechanism:



$$Ph_3C-Cl \longrightarrow Cl^{\ominus} + Ph_3\overset{\oplus}{C} \xrightarrow{H_2\ddot{N}CH_2CO_2^{\ominus}} Ph_3C\overset{\oplus}{N}H_2\ CH_2CO_2^{\ominus} \downarrow Ph_3CNHCH_2COOH$$

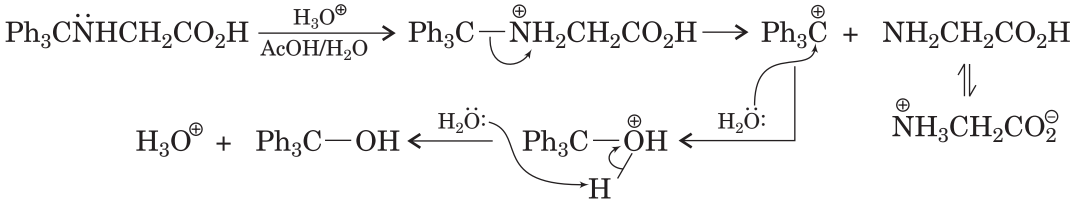
*** Removal of the trityl group** The trityl group can be removed under very mild conditions, either by catalytic hydrogenation or by hydrolysis in the presence of a weak acid.



$$Ph_3CNHCH_2CO_2H \xrightarrow{H_2/Pt} \underset{\text{Triphenylmethane}}{Ph_3CH} + \underset{\text{Glycine}}{H_3\overset{\oplus}{N}CH_2CO_2^{\ominus}}$$

$$Ph_3CNHCH_2CO_2H \xrightarrow[H_2O]{CH_3CO_2H\ (15\%)} \underset{\text{Triphenylmethanol}}{Ph_3COH} + \underset{\text{Glycine}}{H_3\overset{\oplus}{N}CH_2CO_2^{\ominus}}$$

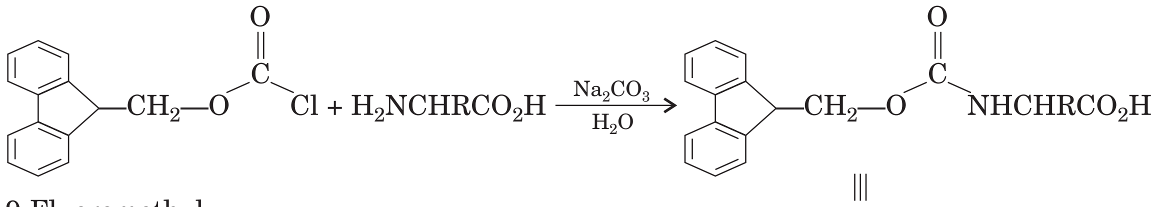
Mechanism:



$$Ph_3C\ddot{N}HCH_2CO_2H \xrightarrow[AcOH/H_2O]{H_3O^{\oplus}} Ph_3C-\overset{\oplus}{N}H_2CH_2CO_2H \longrightarrow Ph_3\overset{\oplus}{C} + NH_2CH_2CO_2H \rightleftharpoons \overset{\oplus}{N}H_3CH_2CO_2^{\ominus}$$

$$Ph_3\overset{\oplus}{C} \xrightarrow{H_2\ddot{O}:} Ph_3C-\underset{H}{\overset{\oplus}{O}H} \xrightarrow{H_2\ddot{O}:} H_3O^{\oplus} + Ph_3C-OH$$

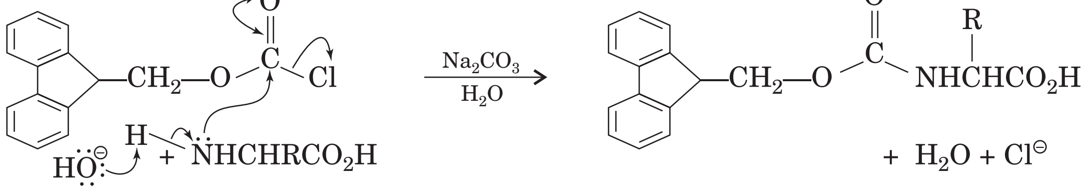
(vi) 9-Fluorenylmethoxycarbonyl group, abbreviated as Fmoc, may also be used as an amino protecting group. It is formed by reacting the amino acid with 9-fluorenylmethyl chloroformate in a nucleophilic acyl substitution reaction.



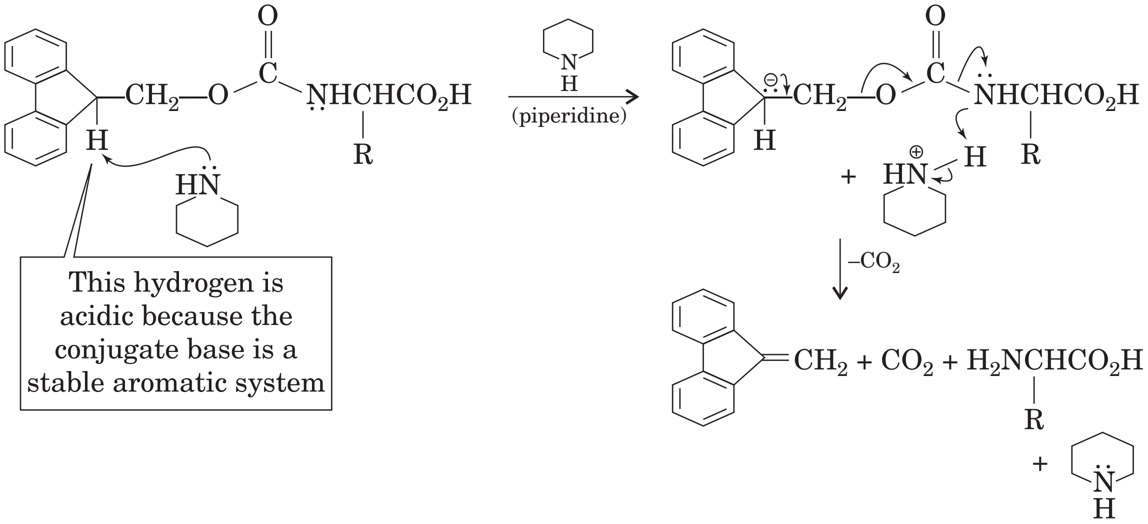
9-Fluoromethyl chloroformate (**Fmoc-Cl**)

Fmoc—NHCHRCO$_2$H
Fmoc-protected amino acid

Mechanism:



While this protecting group is stable to most acids, it can be removed by treatment with a base (NH_3 or an amine) to regenerate the free amino group. Removal by piperidine, for example, may be shown as follows:

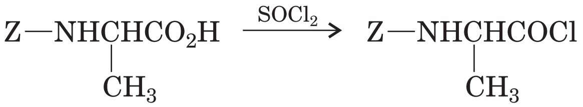


This hydrogen is acidic because the conjugate base is a stable aromatic system

It is to be noted that the **benzoyl group ($\mathrm{Ph{-}\overset{|}{C}{=}O}$) cannot be used as the N-protecting group**. This is because it cannot be removed by hydrolysis without cleavage of the peptide linkages we are trying to make.

Activation of the carboxyl group Activation of the —COOH group of the N-protected amino acid can be carried out by the following ways:

(i) **By converting it to an acid chloride (—COOH → —COCl):** This procedure was used in early peptide synthesis, but acyl chlorides are actually more reactive than necessary. As a consequence their use leads to complicated side reactions. For example:

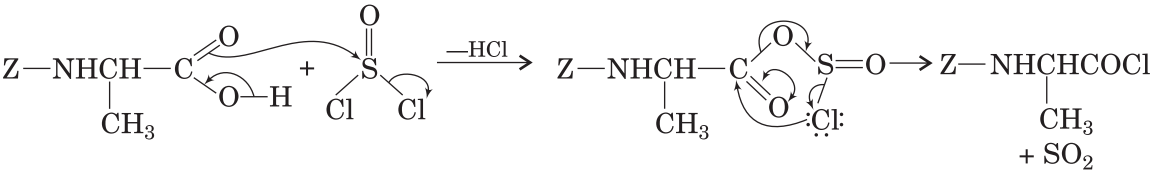


$$\underset{\text{Z-Ala}}{\mathrm{Z{-}NH\underset{\substack{|\\ CH_3}}{C}HCO_2H}} \xrightarrow{SOCl_2} \underset{\text{Acid chloride of Z-Ala}}{\mathrm{Z{-}NH\underset{\substack{|\\ CH_3}}{C}HCOCl}}$$

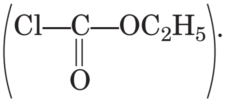
Z-Ala

Acid chloride of Z-Ala

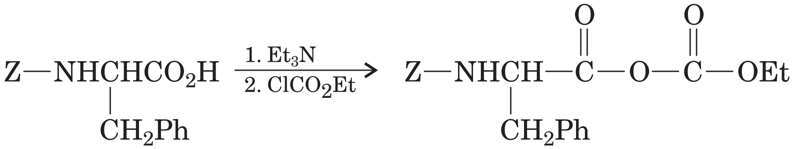
Mechanism



(ii) **By converting it to a mixed anhydride:** A much better method involves conversion of the carboxyl group into a mixed anhydride using ethyl chloroformate



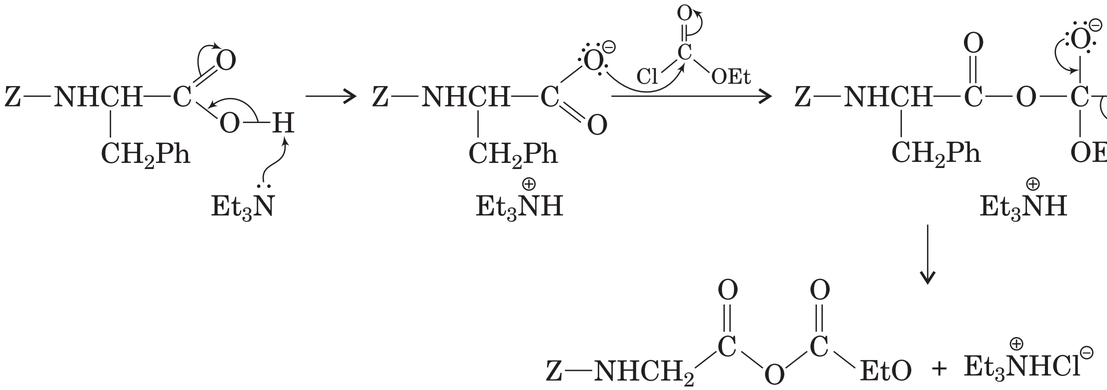
$\left(\mathrm{Cl{-}\overset{}{\underset{\underset{O}{\|}}{C}}{-}OC_2H_5}\right)$. For example:



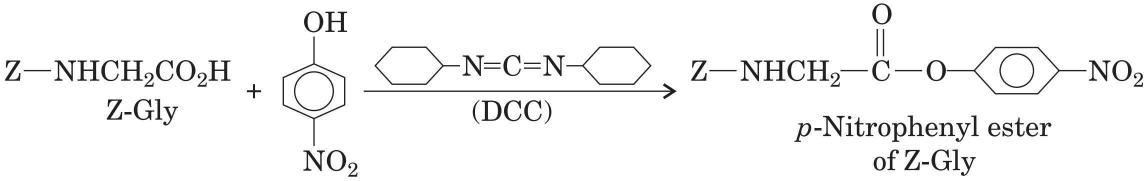
Z-Phe

Mixed anhydride of Z-Phe

Mechanism



(iii) **By converting it to a *p*-nitrophenyl ester (an active ester):** When the Z-protected amino acid is allowed to react with *p*-nitrophenol in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC), the corresponding *p*-nitrophenyl ester is obtained. For example:



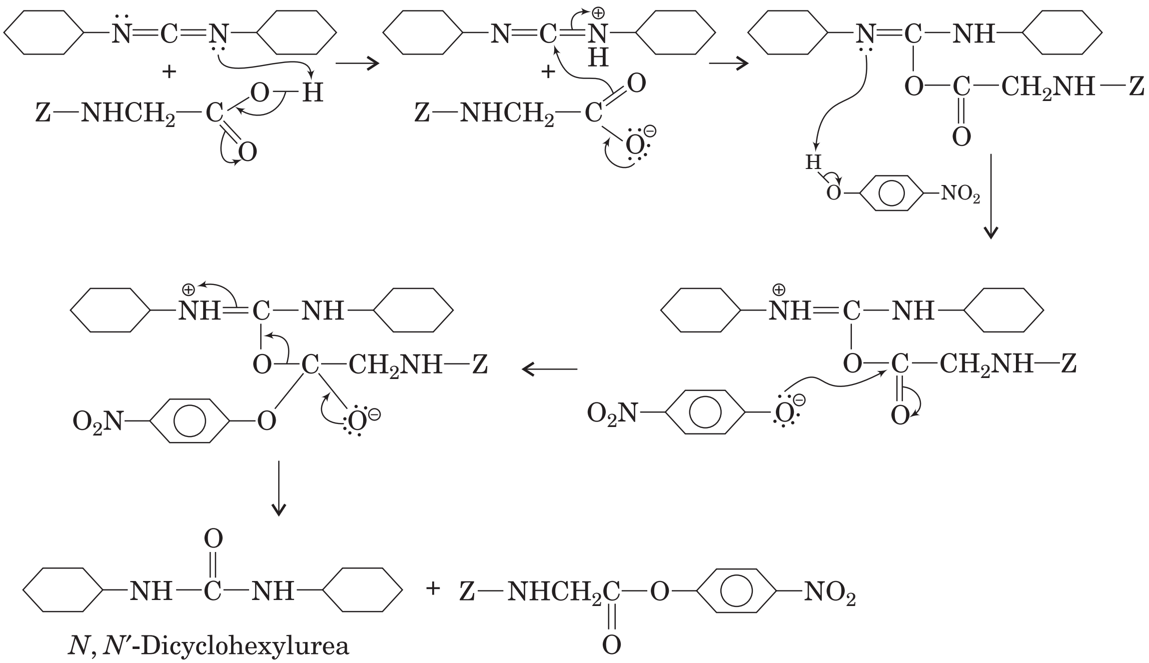
Z-Gly

(DCC)

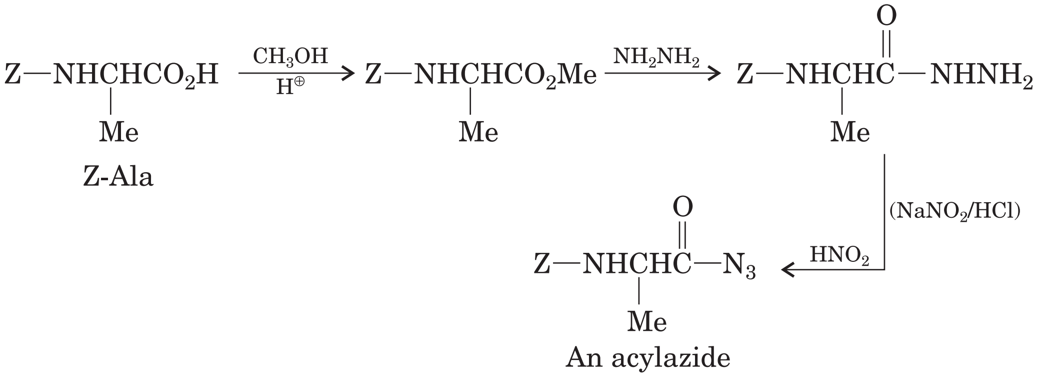
p-Nitrophenyl ester of Z-Gly

p-Nitrophenyl ester are very much reactive because the *p*-nitrophenoxide ion is a much better leaving group.

Mechanism:



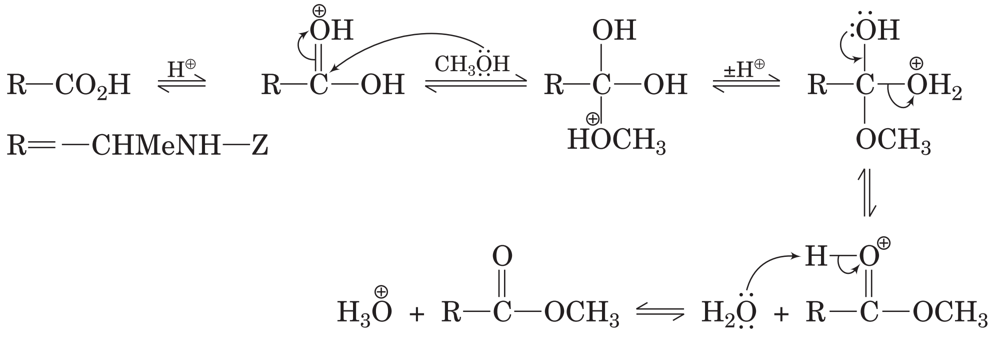
(iv) **By converting it to an acyl azide:** The *Z*-protected amino acid is converted to the corresponding acylazide by first converting it into an ester and then by treating the ester with hydrazine followed by nitrous acid ($NaNO_2/HCl$). For example:



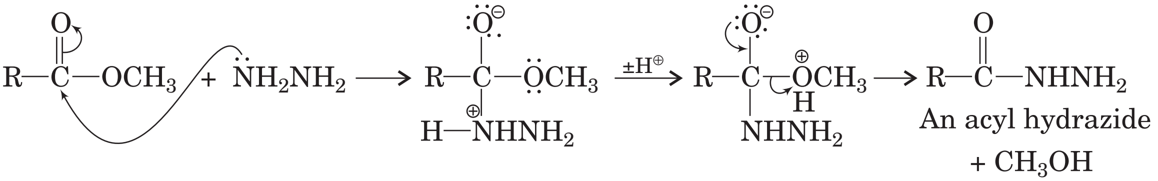
$$\underset{\text{Me}}{\text{Z—NHCHCO}_2\text{H}} \xrightarrow[\text{H}^{\oplus}]{\text{CH}_3\text{OH}} \underset{\text{Me}}{\text{Z—NHCHCO}_2\text{Me}} \xrightarrow{\text{NH}_2\text{NH}_2} \underset{\text{Me}}{\text{Z—NHCH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—NHNH}_2} \xrightarrow[(\text{NaNO}_2/\text{HCl})]{\text{HNO}_2} \underset{\text{Me}}{\text{Z—NHCH}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—N}_3}$$

Mechanism:

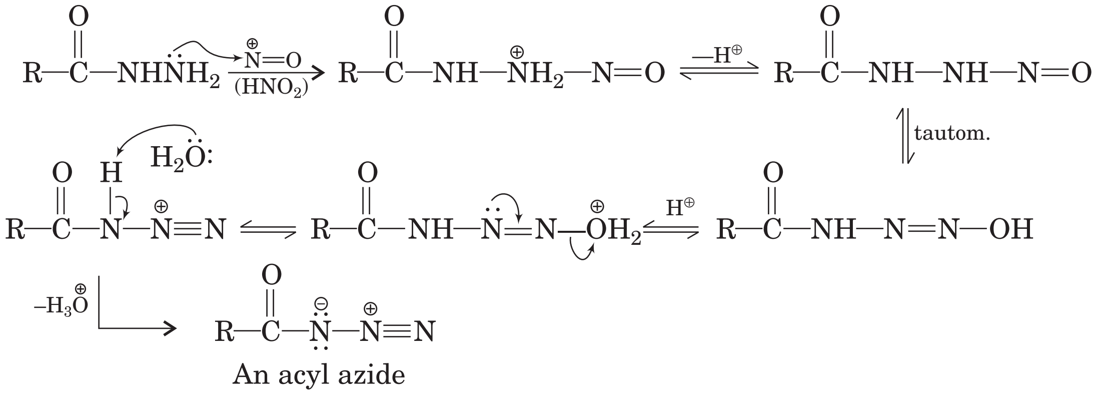
Formation of ester:



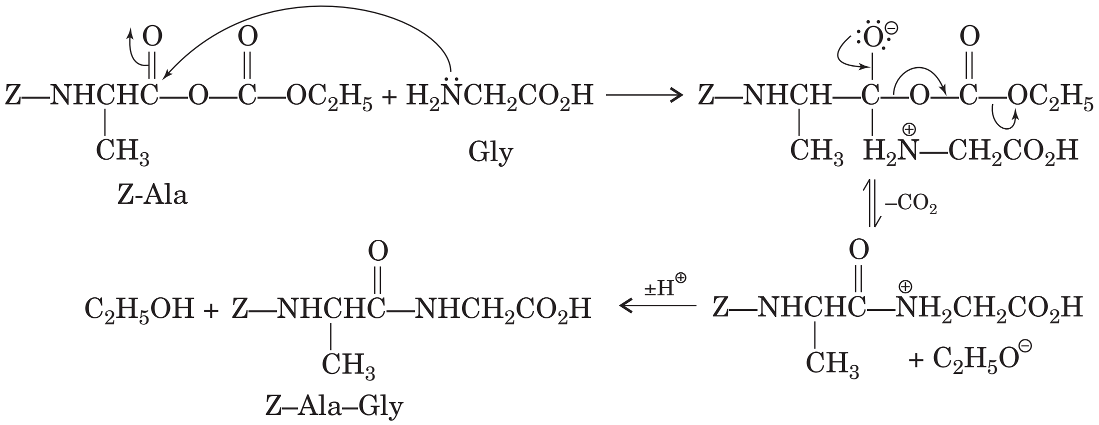
Formation of acyl hydrazide:



Formation of acyl azide:

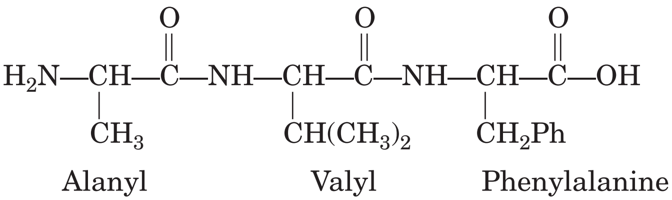


When the protect, activated amino acid is allowed to react with the second amino acid, the second amino acid undergoes acylation leading to the formation of a peptide linkage. For example:



Synthesis of Ala–Val–Phe by the solution-phase method

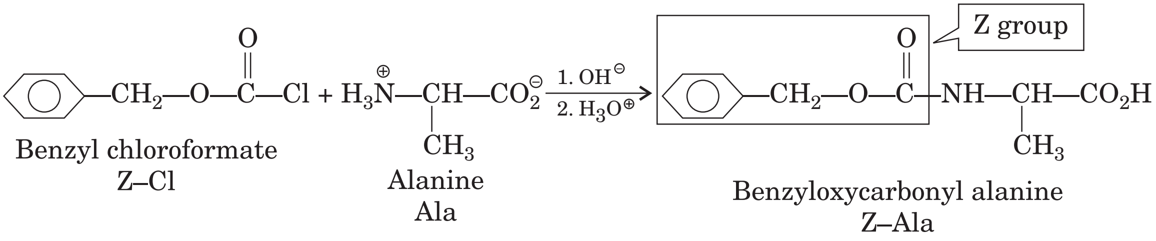
The structure of alanylvalylphenylalanine, a simple tripeptide, is as follows:



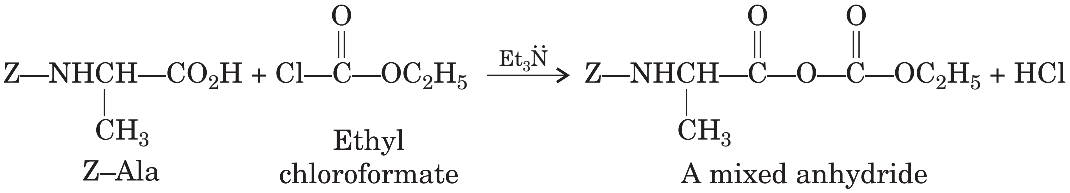
$$\mathrm{H_2N{-}CH(CH_3){-}C({=}O){-}NH{-}CH(CH(CH_3)_2){-}C({=}O){-}NH{-}CH(CH_2Ph){-}C({=}O){-}OH}$$

Ala–Val–Phe

Step 1: Protection of the amino group of alanine

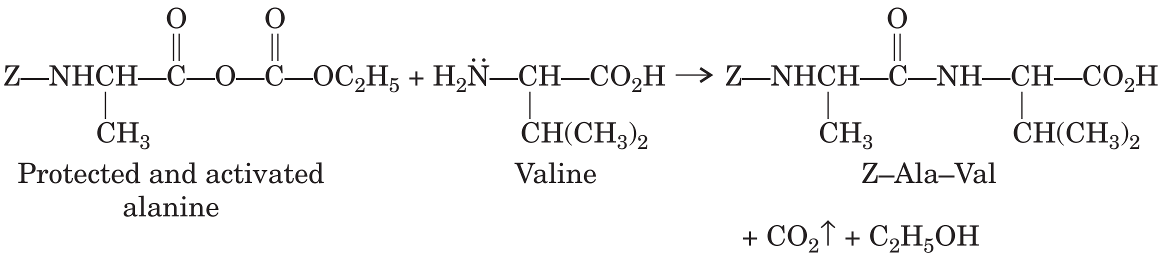


Step 2: Activation of the carboxyl group of Z–Ala



$$\mathrm{Z{-}NHCH(CH_3){-}CO_2H} + \mathrm{Cl{-}C({=}O){-}OC_2H_5} \xrightarrow{Et_3\ddot{N}} \mathrm{Z{-}NHCH(CH_3){-}C({=}O){-}O{-}C({=}O){-}OC_2H_5} + \mathrm{HCl}$$

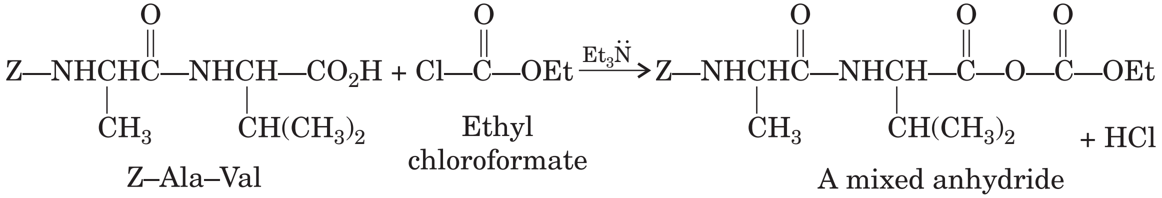
Step 3: Coupling of the next amino acid valine



$$Z-NH\underset{CH_3}{CH}-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-OC_2H_5 + H_2\ddot{N}-\underset{CH(CH_3)_2}{CH}-CO_2H \rightarrow Z-NH\underset{CH_3}{CH}-\overset{O}{\overset{\|}{C}}-NH-\underset{CH(CH_3)_2}{CH}-CO_2H + CO_2\uparrow + C_2H_5OH$$

Protected and activated alanine; Valine; Z–Ala–Val

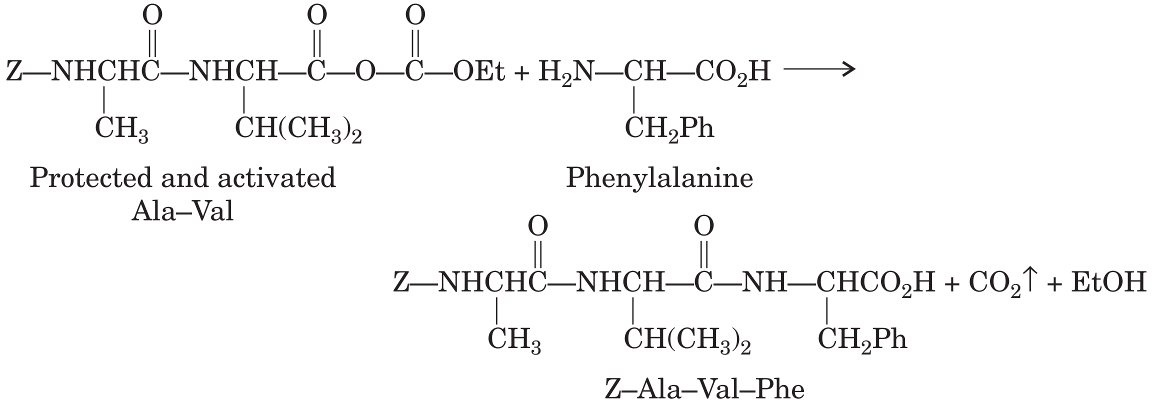
Step 4: Activation of the carboxyl group of Z-Ala-Val



$$Z-NH\underset{CH_3}{CH}\overset{O}{\overset{\|}{C}}-NH\underset{CH(CH_3)_2}{CH}-CO_2H + Cl-\overset{O}{\overset{\|}{C}}-OEt \xrightarrow{Et_3\ddot{N}} Z-NH\underset{CH_3}{CH}\overset{O}{\overset{\|}{C}}-NH\underset{CH(CH_3)_2}{CH}-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-OEt + HCl$$

Z–Ala–Val; Ethyl chloroformate; A mixed anhydride

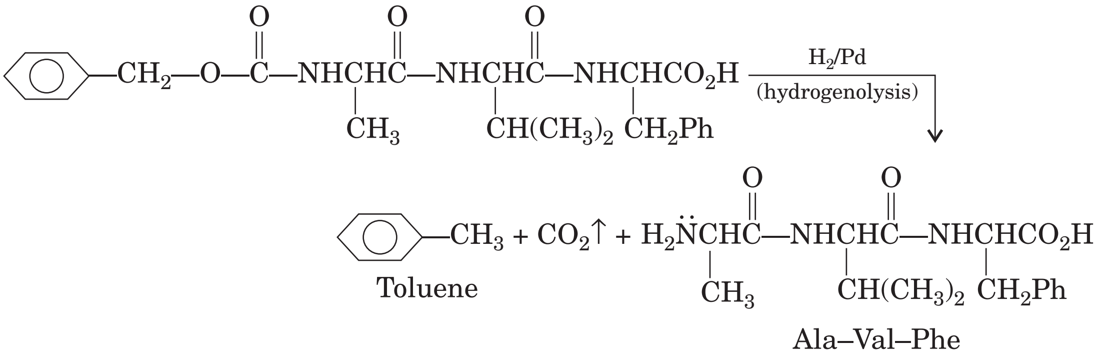
Step 5: Coupling of the next amino acid phenylalanine



$$Z-NH\underset{CH_3}{CH}\overset{O}{\overset{\|}{C}}-NH\underset{CH(CH_3)_2}{CH}-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-OEt + H_2N-\underset{CH_2Ph}{CH}-CO_2H \longrightarrow Z-NH\underset{CH_3}{CH}\overset{O}{\overset{\|}{C}}-NH\underset{CH(CH_3)_2}{CH}-\overset{O}{\overset{\|}{C}}-NH-\underset{CH_2Ph}{CH}CO_2H + CO_2\uparrow + EtOH$$

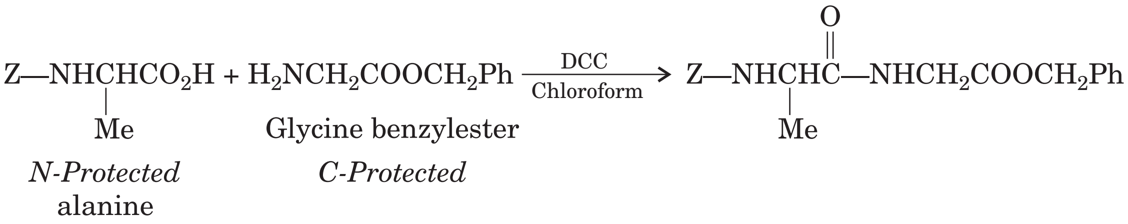
Protected and activated Ala–Val; Phenylalanine; Z–Ala–Val–Phe

Step 6: Removal of the protecting groups



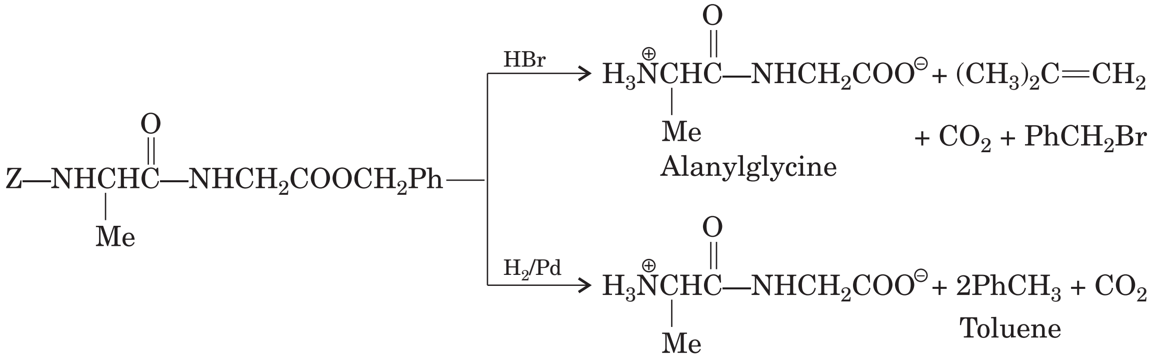
Modification of the classical method for peptide synthesis (use of DCC) Recently, it has been shown that activation of the carboxyl group of the N-protected amino acid followed by its reaction with a second amino acid can be avoided by treating the N-protected amino acid with the second amino acid (with protected carboxyl group) in the presence of dicyclohexylcarbodiimide (DCC). DCC, which acts as an activating as well as dehydrating agent, causes formation of peptide linkage directly. Protection of the carboxyl group of the second amino acid is required because its reaction with DCC is to be prevented. The second amino acid, for example, can be protected by converting it into its benzyl ester, which after the peptide linkage has been generated, can easily be hydrolyzed by anhydrous acid (e.g., HBr). Deprotection can also be effected by H_2/Pd. It is to be noted that these two reagents also cause deprotection of N-terminus.

Formation of peptide linkage:



$$\text{Z—NH}\underset{\text{Me}}{\underset{|}{\text{C}}}\text{HCO}_2\text{H} + \text{H}_2\text{NCH}_2\text{COOCH}_2\text{Ph} \xrightarrow[\text{Chloroform}]{\text{DCC}} \text{Z—NH}\underset{\text{Me}}{\underset{|}{\text{C}}}\text{H}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—NHCH}_2\text{COOCH}_2\text{Ph}$$

Complete deprotection:

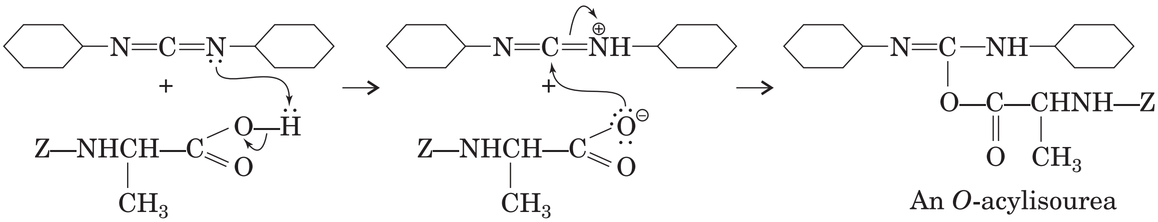


$$\text{Z—NH}\underset{\text{Me}}{\underset{|}{\text{C}}}\text{H}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—NHCH}_2\text{COOCH}_2\text{Ph} \xrightarrow{\text{HBr}} \text{H}_3\overset{\oplus}{\text{N}}\underset{\text{Me}}{\underset{|}{\text{C}}}\text{H}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—NHCH}_2\text{COO}^{\ominus} + (\text{CH}_3)_2\text{C}{=}\text{CH}_2 + \text{CO}_2 + \text{PhCH}_2\text{Br}$$

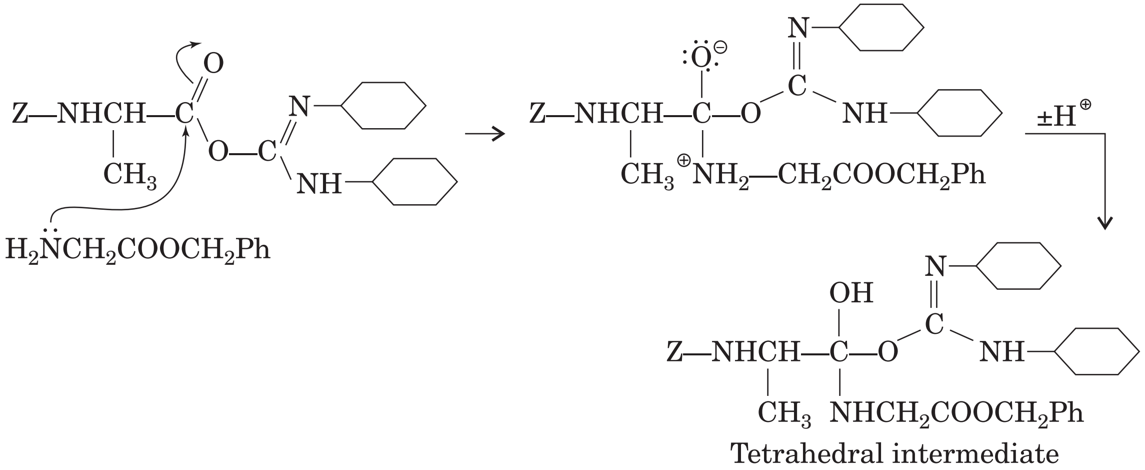
$$\text{Z—NH}\underset{\text{Me}}{\underset{|}{\text{C}}}\text{H}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—NHCH}_2\text{COOCH}_2\text{Ph} \xrightarrow{\text{H}_2/\text{Pd}} \text{H}_3\overset{\oplus}{\text{N}}\underset{\text{Me}}{\underset{|}{\text{C}}}\text{H}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{—NHCH}_2\text{COO}^{\ominus} + 2\text{PhCH}_3 + \text{CO}_2$$

Mechanism The mechanism of peptide formation in the presence of DCC involves the steps as follows:

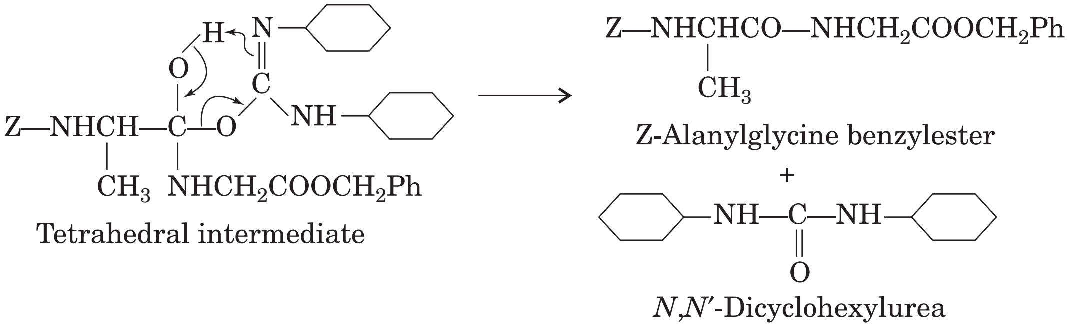
Step 1 The *N*-protected amino acid adds to one of the double bonds of DCC to yield an *O*-acylisourea (an activated carboxylic acid derivative).



Step 2 The *O*-acylisourea, which resembles a carboxylic acid anhydride, acts as a powerful acylating agent. The C-protected amino acid adds to the carbonyl group of the *O*-acylisourea to form a tetrahedral intermediate.



Step 3 The tetrahedral intermediate finally dissociates to an amide (the dipeptide) and *N*,*N′*-dicyclohexylurea (DCU).



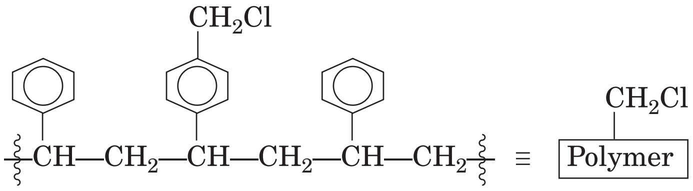
Methods like this can be repeated over and over with the addition of a new amino acid each time. In this way the hormone oxytocin was synthesized by *Vincent du Vignenand* (Nobel Prize recipient of 1955).

10.2.7.2 Solid-Phase Peptide Synthesis

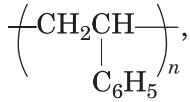
The solution-phase peptide synthesis actually works better for small peptides. This method if not suitable for large proteins because a large number of chemical reactions and purifications are required for which the overall yield becomes so small as to be unusable. Furthermore, several months (or years) are required to complete so many steps. For these reasons, solid-phase peptide synthesis is usually preferred for larger peptides and proteins.

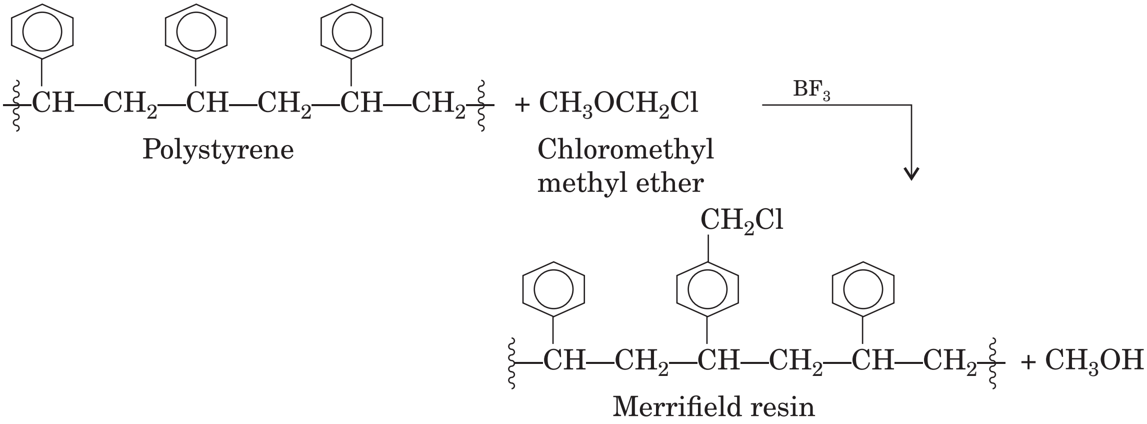
Robert Bruce Merrifield of Rockefeller University developed a method in 1962 for synthesizing peptides without having to purify the intermediates. In this method, peptide coupling and deprotection are carried out not in homogeneous solution but at the surface of an insoluble polymer, or *solid support*. After each amino acid is added, the excess reagents are washed away by rinsing the bead with solvent. Merrified synthesized *ribonuclease* (an enzyme containing 124 amino acids) involving 369 chemical reactions and 11931 steps in just 6 weeks and the overall yield of the protein is 17% (in every reaction the yield is > 99%). Merrifields work in solid-phase peptide synthesis won the Nobel Prize in Chemistry in the year 1984.

The solid support is a special polystyrene bead in which some (about 10%) of the aromatic rings have chloromethyl groups. The polymer is often called the *Merrifield resin*.



Merrifield resin Abbreviation

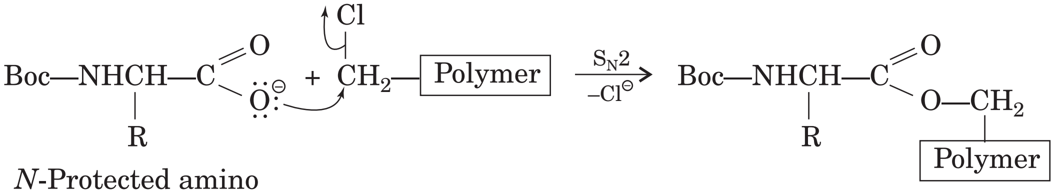
The Merrifield resin is prepared by treating polystyrene  $\left(\underset{\displaystyle C_6H_5}{CH_2CH}\right)_n$, with chloromethyl methyl ether, CH_3OCH_2Cl and tin(IV) chloride or BF_3 (a Lewis acid).



The important difference between the solution-phase and the solid phase peptide synthesis is that the solid-phase synthesis is done in the opposite direction, i.e., from C-terminus to N terminus or right to left as we write the peptide. The first step involves attachment of the last amino acid (the C-terminus) to the solid support.

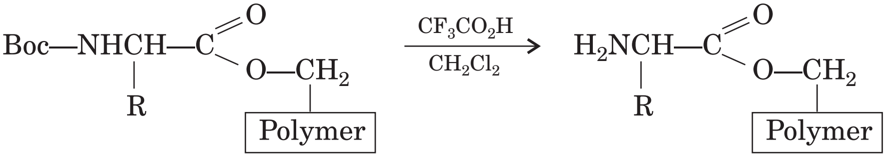
The solid-phase peptide synthesis involves the steps as follows:

Step 1 (attachment of the *N*-protected C-terminal amino acid) The *N*-protected (the Boc group in the protecting group) C-terminal amino acid of the desired peptide is anchored to the polymer by shaking a solution of its salt in an organic solvent with the insoluble polymer. The chloromethyl groups on the polymer are reactive toward S_N2 attack and because of this, the carboxylate group of the *N*-protected amino acid displaces chloride, giving an amino acid ester of the polymer. In fact, the polymer serves as the alcohol part of an ester protecting group for the carboxyl end of the *C*-terminal residue



N-Protected amino acid (salt)

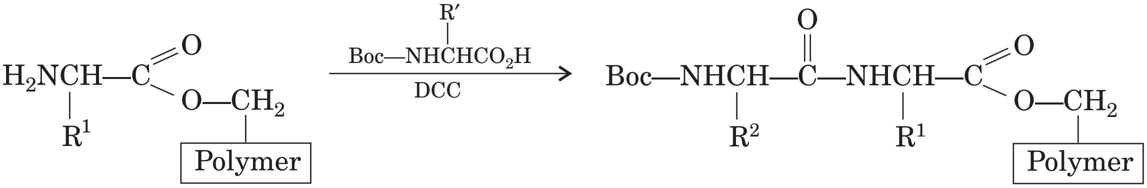
Step 2 (removal of the Boc group) The Boc group is removed by brief treatment with trifluoroacetic acid (TFA), CF_3CO_2H.



Polymer-bound amino acid

After the resin has been washed, the C-terminal amino acid is ready for coupling.

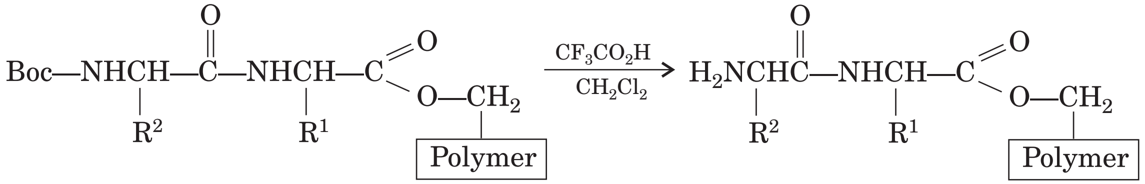
Step 3 (peptide coupling using DCC) The polymer-bound C-terminal amino acid is coupled to an *N*-protected amino acid by using *N*,*N*′-dicyclohexylcarbodiimide (DCC).



N-Protected, polymer-bound dipeptide

Excess reagent and *N*,*N*′-dicyclohexylurea are washed away from the polymer after coupling is complete.

Step 4 (removal of the Boc group) The Boc group is removed by treatment with trifluoroacetic acid, and after washing, the polymer is now ready for coupling with another *N*-protected amino acid residue involving DCC as the coupling agent.

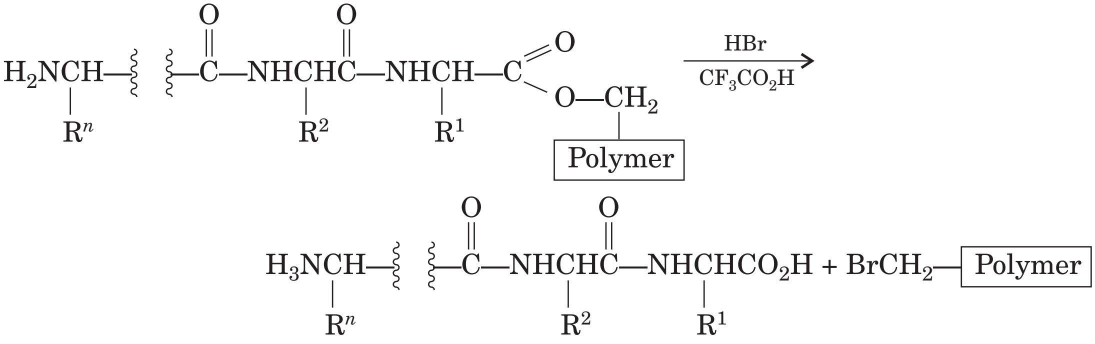


$$\text{Boc—N}H\underset{R^2}{\underset{|}{CH}}\text{—}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^1}{\underset{|}{CH}}\text{—}C(=O)\text{—O—CH}_2\text{—}\boxed{\text{Polymer}} \xrightarrow[CH_2Cl_2]{CF_3CO_2H} H_2N\underset{R^2}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^1}{\underset{|}{CH}}\text{—}C(=O)\text{—O—CH}_2\text{—}\boxed{\text{Polymer}}$$

Polymer-bound dipeptide

Steps 3 and 4 may be repeated to introduce as many amino acid residue as desired.

Steps 5 (removal of the peptide from the polymer) When all the amino acid residues are coupled, i.e., the desired peptide is completely assembled, it is removed from the resin by treatment with hydrogen bromide in CF_3CO_2H under conditions mild enough not to affect the amide linkages.



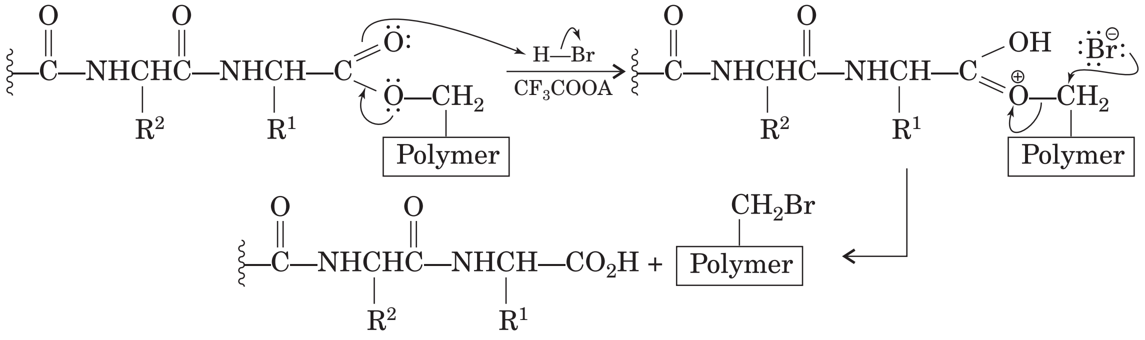
$$H_2N\underset{R^n}{\underset{|}{CH}}\text{—}\wr\ \wr\text{—}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^2}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^1}{\underset{|}{CH}}\text{—}C(=O)\text{—O—CH}_2\text{—}\boxed{\text{Polymer}} \xrightarrow[CF_3CO_2H]{HBr}$$

$$H_3N\underset{R^n}{\underset{|}{CH}}\text{—}\wr\ \wr\text{—}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^2}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^1}{\underset{|}{CH}}CO_2H + BrCH_2\text{—}\boxed{\text{Polymer}}$$

Peptide

Expulsion of the completed peptide from the solid support may also be accomplished with anhydrous HF, which also removes the last Boc group.

Mechanism for the cleavage of peptide from the polymer:



$$\wr\text{—}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^2}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^1}{\underset{|}{CH}}\text{—}C(=\ddot{O}\text{:})\text{—}\ddot{O}\text{—CH}_2\text{—}\boxed{\text{Polymer}} \xrightarrow[CF_3COOA]{H\text{—}Br} \wr\text{—}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^2}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^1}{\underset{|}{CH}}\text{—}C(\text{OH})=\overset{\oplus}{O}\text{—CH}_2\text{—}\boxed{\text{Polymer}}\ \ :\ddot{Br}:^{\ominus}$$

$$\longrightarrow \wr\text{—}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^2}{\underset{|}{CH}}\overset{O}{\overset{\|}{C}}\text{—NH}\underset{R^1}{\underset{|}{CH}}\text{—}CO_2H + \overset{CH_2Br}{\boxed{\text{Polymer}}}$$

Merits of the Merrifield method are as follows:

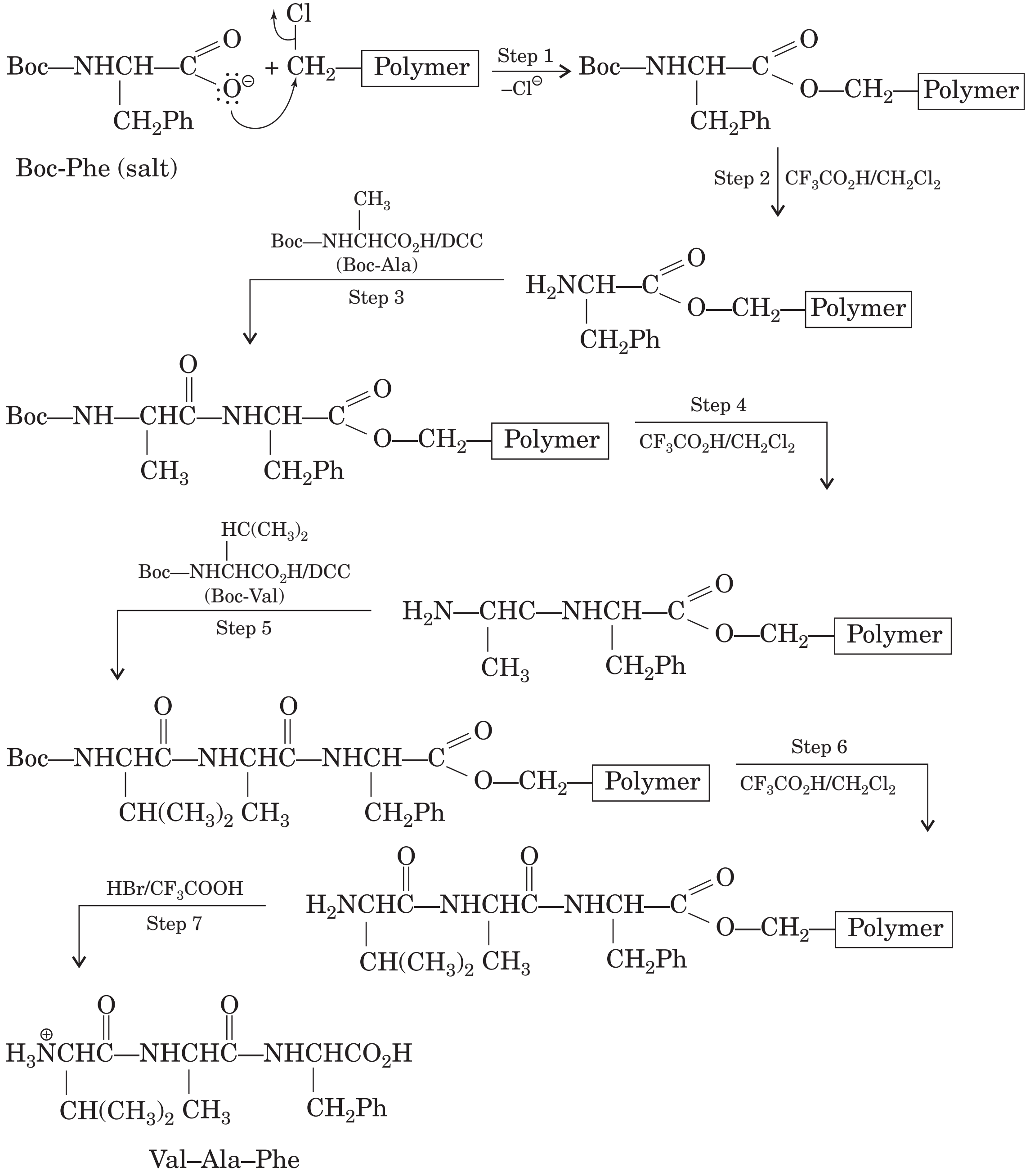
(a) The impurities are readily removed by washing with a solvent since they are not bonded to the polymer.

(b) The separation of intermediates (which is responsible for low yield) are not required.

(c) The yield is of appreciable amount.

An example of solid-phase synthesis

The synthesis of Val–Ala–Phe by solid-phase method of Merrifield may be outlined as follows (the synthesis is started with commercially available salt of Boc-protected phenylalanine):



10.2.8 Classification of Proteins

Proteins may be classified according to their chemical composition, shape and function.

According to chemical composition, they are classified as *simple* and *conjugated* proteins. Simple proteins are those that hydrolyze to yield only amino acids. Examples of simple proteins are insulin, ribonuclease, oxytocin, etc. On the other hand, conjugated proteins are those which are bonded to a nonprotein prosthetic group such as a sugar, a nucleic acid, a lipid, or some other group. Class, prosthetic group and examples of some conjugated proteins are given below:

Class	Prosthetic Group	Examples
1. Glycoproteins	Carbohydrates	Mucin; γ-Globulin; Interferon
2. Nucleoproteins	Nucleic acids	Viruses; Ribosomes
3. Lipoproteins	Lipids, cholesterol	High-density lipoprotein (HDL)
4. Metalloproteins	A complexed metal	Hemoglobin; Cytochromes
5. Phosphoproteins	Phosphate group	Casein of milk
6. Flavoproteins	Flavin nucleotide	*Succinate dehydrogenase* (enzyme)

Proteins are classified as fibrous and globular proteins according to their shape and function:

Fibrous proteins In this class of proteins, large molecules wound around each other to produce thread which tend to lye side by side to form fibres. In some cases, they held together at many points by hydrogen bonding. Because of this, the intermolecular forces that must be overcome by a solvent are very strong, and that's why they are insoluble in water. They function mainly as the chief structural material of animal tissues, a function to which their insolubility and fibre-forming tendency suit them. Some examples of fibrous proteins are *Keratin*, in skin, hair, nails, wool, horn and feathers; *collagen*, in tendons; *myosin* in muscle and *fibroin*, in silk. Fibrous proteins are also called *structural proteins*.

Globular proteins In this class of proteins, large protein molecules are folded into compact units that often approach spheroidal shapes. The folding takes place in such a way that the lipophilic, i.e., hydrophobic parts (R groups) are turned inward, toward each other, and away from water, whereas the hydrophilic parts (e.g, charged groups) are turned outward to form H-bonding with water molecules. Because of this, globular proteins are soluble in water. Since areas of contact between molecules are small, the intermolecular forces are relatively weak. Globular proteins serve a variety of functions related to the maintenance and regulation of the life process requiring mobility and hence solubility. Examples of globular proteins are enzymes; hormones (e.g., *insulin*, from the pancreas), *albumin* in eggs; *hemoglobin*, which transports oxygen from lungs to the tissues; *thyroglobulin* (from the thyroid gland) and *fibrinogen* which becomes converted into the insoluble, fibrous protein *fibrin*, and thus causes blood clotting (coagulation) that prevents excessive bleeding when a blood vessel is injured.

10.2.9 Levels of Protein Structure

The various levels of protein structure are as follows:

1. **Primary structure:** The primary structure of a protein is the covalently bonded structure of the molecule which includes the sequence of the amino acid residues, together with any disulphide bridges. The primary structure determines all the properties of protein directly or indirectly. It is the primary structure on which any folding, hydrogen bonding or catalytic activity depends.
2. **Secondary structure:** The secondary structure of protein refers to the shape in which the long amino acid chains exist, i.e., the secondary structure of a protein is, in fact, the conformational relationship of nearest neighbour amino acids with respect to each other. The H-bonding between an N—H of one amino acid residue and the O═C of another properly situated amino acid residue is greatly responsible for the secondary structure of proteins. Depending upon the size of R group, the following three secondary structures are possible:

(a) Flat sheet structure Protein chains having side chain of smaller size (say H) are regarded as fully extended in a *zig-zag* manner with alternate side chains being on the same side situated at a fixed distance. Such extended peptide chains lie side by side ; each one of them is joined to the two neighbouring chains through intermolecular hydrogen bonds. This results in formation of what is called a flat sheet structure. This is shown in the figure below (Figure 10.3):

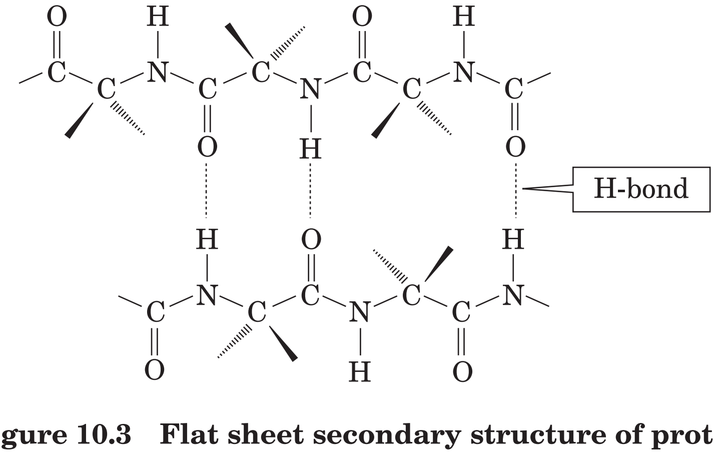
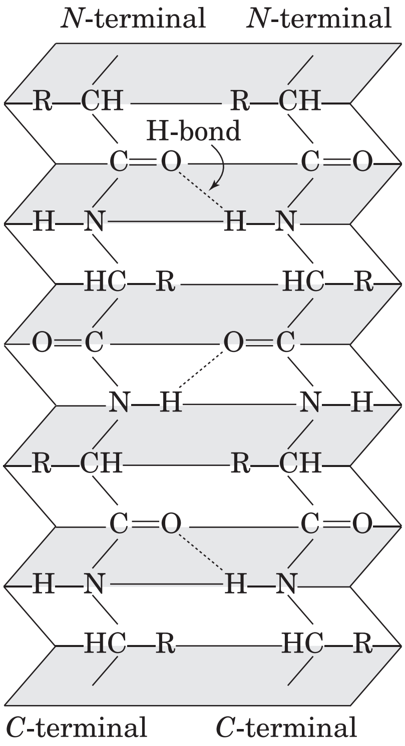


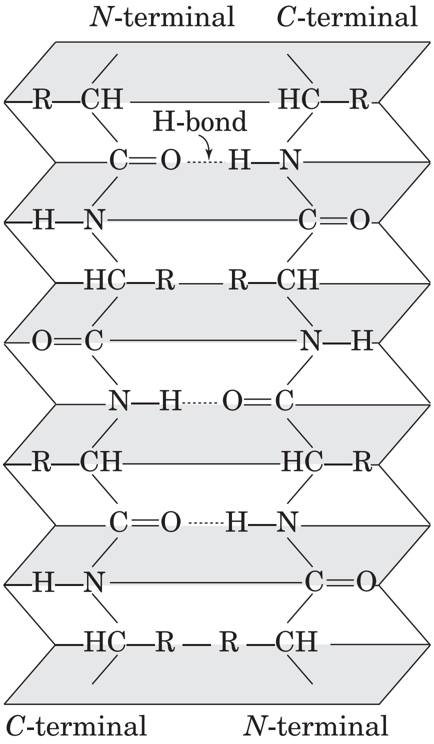
Figure 10.3 Flat sheet secondary structure of protein

Synthetic polyglycine, because of the presence of no side chain, is expected to have flat sheet structure.

(b) Pleated sheet structure When there are side chains of moderate size, the peptide chain contracts a little in order to accommodate them. This results in what is called the pleated sheet structure or the *beta* arrangement of the protein. In this structure, the peptide chains lie side-by-side in an open structure, with inter-chain H-bonding between the N—H and C═O groups. *Parallel* pleated sheets have chains extended in the same direction, all with their *N*-terminal residue starting at the same end. *Antiparallel* pleated sheets have their chains extended in opposite directions. The α-carbons rotate slightly out of the plane of sheet to decrease repulsions between the bulky R groups, giving rise to the crimps or pleats. In both the pleated sheets, the R groups alternate positions above and below the sheet.



Parallel pleated sheet



Antiparallel pleated sheet

(c) α-Helical structure When the side chains of the peptide are quite large, a quite different structure is assumed by the peptide chain. The whole peptide chain, in such cases, is coiled into a right-handed spiral form known as α-helix, with R groups all extended away from the axis of the helix (Figure 10.4). As all the naturally occurring amino acids have L-configuration, all protein helices have been found to be right handed. This helical conformation with about 3.6 amino acid per turn permits each carbonyl oxygen to be hydrogen-bonded to each amide N—H bond and as a result, the arrangement is stabilized.

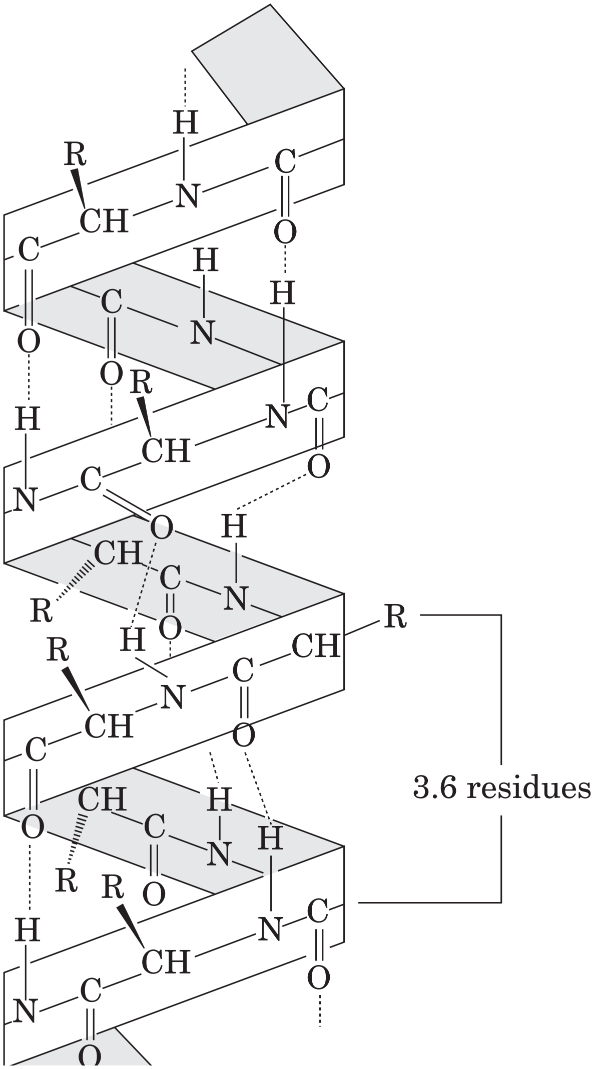


Figure 10.4 a-Helix conformation of a typical protein

The α-helical structure is found in many proteins. It is the predominant structure of the polypeptide chains of fibrous proteins like *myosin* (the protein of muscle), and of *α-Keratin* (the protein of hair), unstretched wool and nails.

A protein may or may not have the same secondary structure throughout its length. Some parts may be curled into an α-helix, while other parts may have pleated sheet structure. Some parts may have no secondary structure at all. Such a structureless part is called a *random coil*. For example, most of the globular proteins contain segments of pleated sheet or α-helix conformation separated by kinks of random coil, which, in fact, allows the molecule to fold into its globular shape.

3. **Tertiary structure:** The tertiary structure of a protein is its complete three-dimensional conformation that arises from further folding of its peptide chains. It includes all the secondary structures and all the kinks and folds in between. The style in which the chain is folded affects both the physical properties of a protein and its biological function. The two most important shapes taken up by the proteins are globular (spherical shape) and fibrous (rod like shape).

The attractive forces responsible for the tertiary structure of proteins are as follows:

(i) Very weak van der Waals forces caused by side-chain R groups (e.g., interaction between the tryptophan and phenylalanine residues).

(ii) Additional H-bonding between side-chain containing —NH— or $CONH_2$ and —OH groups (e.g., H-bonding between the —OH group of serin and the —NH— group of tryptophan or the $—CONH_2$ group of asparagin).

(iii) Intramolecular salt like dipolar bonding (electrostatic attraction) between 'extra' —COOH and $—NH_2$ groups at different sites [e.g., electrostatic attraction between the $—CH_2COO^{\ominus}$ group of aspartic acid and $—(CH_2)_4\overset{\oplus}{N}H_3$ group of lysine].

(iv) Disulphide covalent bonding (—S—S—) or disulphide cross linkages between the loops of the peptide chain between two cysteine residues.

These attractive forces are shown in the following figure (Figure 10.5).

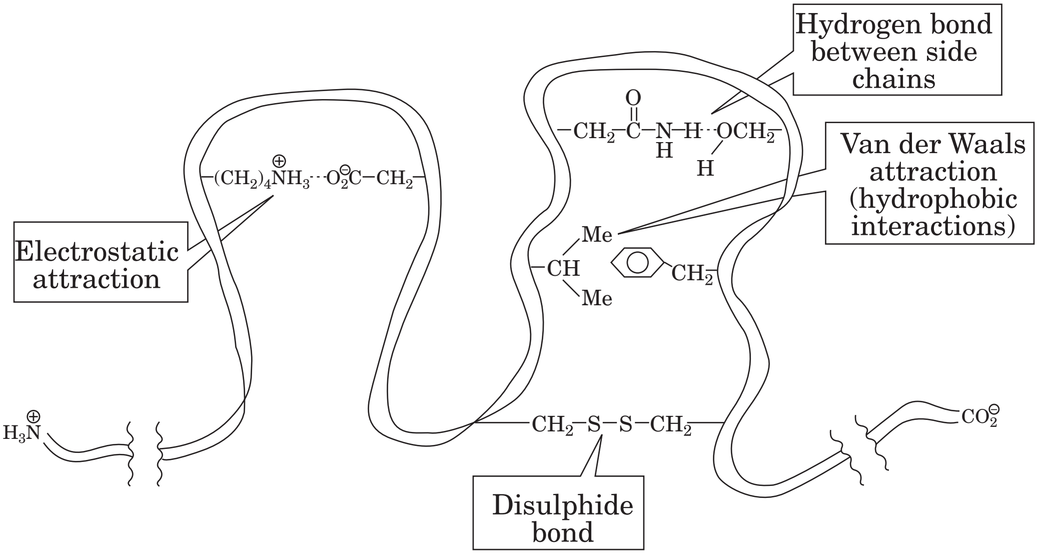

Hydrogen bond between side chains
Van der Waals attraction (hydrophobic interactions)
Electrostatic attraction
Disulphide bond
$-(CH_2)_4\overset{\oplus}{N}H_3 \cdots O_2^{\ominus}C-CH_2-$
$-CH_2-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-H\cdots OCH_2-$
H
Me
CH
Me
CH_2
$CH_2-S-S-CH_2$
$H_3\overset{\oplus}{N}$
$CO_2^{\ominus}$

Figure 10.5 Stabilizing interactions responsible for the tertiary structure of a protein

It is to be noted that coiling of an enzyme (a protein) can produce important catalytic effects. Polar and hydrophilic (water-loving) side chains are oriented towards the outside of the globule, while the nonpolar and hydrophopic (water-hating) groups are oriented towards the interiors. Due to coiling in the proper conformation, an enzyme's **active site** (the region that binds the substrate and catalyzes the reaction) is created. In fact, a reaction taking place at the active site in the interior of an enzyme may proceed under anhydrous, nonpolar conditions when, however, the system remains dissolved in water.

4. **Quaternary Structure:** Some proteins are assemblies of two or more polypeptide chains. The individual chains are called subunits. A protein with one, two, three and four subunits are called a monomer, dimer, trimer and tetramer, respectively. The quaternary structure of a protein describes the way the subunits are arranged with respect to each other. The subunits may be identical or different. The subunits are held together by the same kinds of interaction that hold the individual protein chains in a particular three-dimensional conformation — van der Waals attractions, H-bonding and electrostatic forces of attractions. Hemoglobin, for example, consists of four peptide chains fitted together to form a globular protein. It has two different kinds of subunits (two of each kind).

10.2.10 Denaturation of Protein

Alternation or loss of the unique three-dimensional conformational state of a protein by destroying its highly organized tertiary structure is called *denaturation of a protein*. It completely or partially unfolds into random structures without simultaneous cleavage of the peptide chain. Anything that breaks the bonds maintaining the three-dimensional shape of the protein will cause the protein to denature. The bonds broken are those responsible for the secondary, tertiary and, if present, quaternary structures. Because these bonds are weak, proteins undergo easy denaturation.

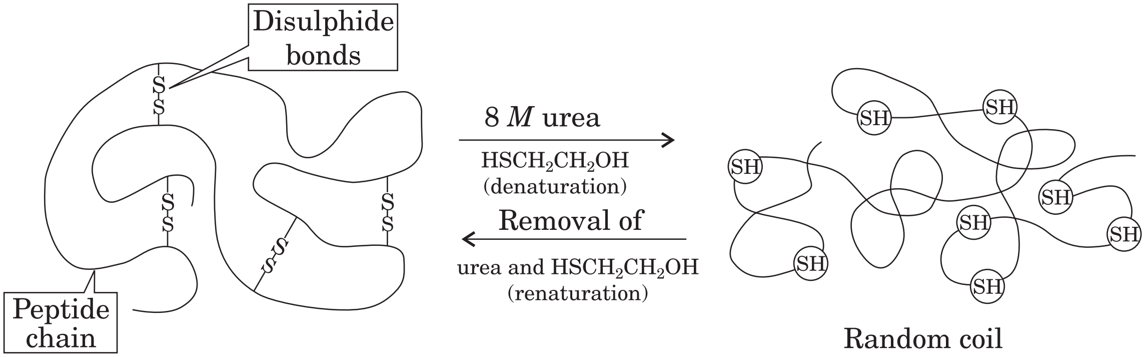
The different kinds of denaturing agents and the process involved in each case may be listed in the table below.

Denaturing agent	Mechanism of action
1. **Proteins can be denatured by heat, UV radiation or shaking.**	Each of these agents increases molecular motion, which can disrupt the attractive forces (like H-bonds and van der Waals forces), resulting in precipitation. A well-known example is the change that takes place to the white of an egg (albumin) when it is heated
2. **Changing the pH denatures proteins.**	This is because it changes the charges on many of the side chains. Also, pH change disrupts H-bonding and electrostatic attractions causing coagulation. A well-known example is the curdling of milk. Milk turns sour because of the bacterial conversion of carbohydrates to lactic acid. When the pH becomes strongly acidic, soluble milk proteins are denatured and precipitate. This process is called curdling.

3. Proteins can be denatured by organic solvents or detergents like sodium dodecycle sulphate.	Denaturation is caused by associating with the nonpolar groups of the protein thereby disrupting the normal hydrophobic interactions.
4. **Certain reagents such as guanidine hydrochloride and urea denature proteins.**	These reagents denature proteins by forming H-bonds to protein (replacing intramolecular H-bonds) causing precipitation.
5. **Denaturation of proteins by heavy metal ions.**	Heavy metals ions like Hg^{2+}, Pb^{2+}, Ag^{+}, Tl^{+}, Cd^{2+}, etc. denature proteins by disrupting salt bridges causing precipitation.

• Reversible and Irreversible Denaturation

If a protein can regain its native state when the denaturing influence is removed, i.e., if renaturation is possible, then the denaturation process is called reversible denaturation. For example, the enzyme *ribonuclease* can be denatured by treating with 2-mercaptoethanol and 8 *M* urea. After the urea is removed, and the cysteine —SH groups are allowed to reoxidize back to disulphides, the protein spontaneously reassures its original (*native*) conformation and regains its activity.



Native conformation of a protein

Random coil (reduced and denatured protein)

If a protein cannot regain its native state when the denaturing influence is removed, i.e., if renaturation is not possible, then the denaturation process is called irreversible denaturation. For example, when egg white is heated, the soluble globular proteins (called albumins) present in egg unfold and coagulate, i.e., undergo denaturation to yield a solid rubbery mass of insoluble fibrous proteins. However, when heating is stopped, regeneration does not take place.

SOLVED PROBLEMS

1. **Explain why the Edman degradation is usually more preferred over the Sanger method for sequencing peptides. [C.U. 2013]**

Solution In Edman degradation, only the N-terminal amino acid is cleaved; the rest of the peptide chain remains intact for further degradation. Thus, sequence determination is possible by repeating the process. In Sanger method, on the other hand, hydrolytic cleavage brings about the complete breakdown of the peptide to the component amino acids and as a result, the amino acid sequence cannot be easily determined. Because of this, Edman degradation is usually more preferred over the Sanger method.

2. **A tetrapeptide of unknown sequence, on amino acid analysis, was found to contain Val, Gly, Phe and Ala in equimolar ratios. Predict the primary structure of the tetrapeptide from the following three observations: (i) Ala is the N-terminal amino acid, (ii) the tetrapeptide is hydrolyzed to yield a number of fragments, one of which is a tripeptide composed by Gly, Phe, and Ala and (iii) a dipeptide containing val and gly is also present in the hydrolysis mixture.**

Solution Since Ala is the N-terminal amino acid and the tripeptide obtained on partial hydrolysis contains Ala but not Val, Val must be the C-terminal amino acid. Since Val and Gly are found together in the same dipeptide present in the hydrolysis mixture, Gly must be the third amino acid residue, counting from the N-terminus. Therefore, the primary structure of the tetrapeptide is

Ala – Phe – Gly – Val

3. **When heated with peroxy formic acid, the peptide hormone vasopressin is partially hydrolyzed. The following fragments are isolated. Predict the structure of vasopressin.**

Phe – Gln – Asn **Pro – Arg – Gly · NH_2** **Cys –Tyr – Phe**

Asn – Cys – Pro – Arg **Tyr – Phe – Gln – Asn**

Solution The complete structure of the peptide vasopressin may be obtained if we match the overlapping regions of the fragments obtained on hydrolysis.

Cys – Tyr – Phe

Phe – Gln – Asn

Tyr – Phe – Gln – Asn

Asn – Cys – Pro – Arg

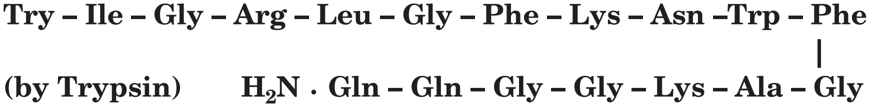
Pro – Arg – Gly – NH_2

C-terminus (amide form)

Cys – Tyr – Phe – Gln – Asn – Cys – Pro – Arg – Gly – NH_2

4. Predict the peptides that would result from cleavage by the indicated reagent.

(a)

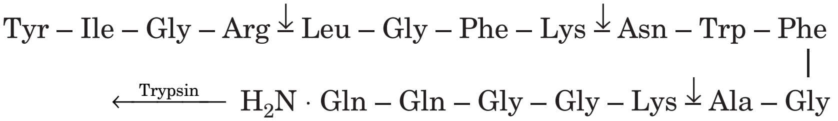


$$\begin{array}{r} \textbf{Try – Ile – Gly – Arg – Leu – Gly – Phe – Lys – Asn –Trp – Phe} \\ | \\ \textbf{H}_2\textbf{N}\cdot\textbf{Gln – Gln – Gly – Gly – Lys – Ala – Gly} \end{array}$$

(by Trypsin)

(b) Leu – Gly – Ser – Met – Phe – Pro – Tyr – Gly – Val (by chymotrypsin)

Solution (a) Trypsin cleaves a peptide chain at the carboxyl groups of the basic amino acids lysine (Lys) and arginine (Arg). Therefore, trypsin cleaves the chain at the following points (shown by arrow) to give four (I–IV) peptides:



$$\begin{array}{r} \text{Tyr – Ile – Gly – Arg} \downarrow \text{Leu – Gly – Phe – Lys} \downarrow \text{Asn – Trp – Phe} \\ | \\ \xleftarrow{\text{Trypsin}} \text{H}_2\text{N}\cdot\text{Gln – Gln – Gly – Gly – Lys} \downarrow \text{Ala – Gly} \end{array}$$

$$\underset{\text{I}}{\text{Tyr – Ile – Gly – Arg}} + \underset{\text{II}}{\text{Leu – Gly – Phe – Lys}} +$$

$$\underset{\text{III}}{\text{Asn – Trp – Phe – Gly – Ala}} + \underset{\text{IV}}{\text{Lys – Gly – Gly – Gln – Gln}\cdot\text{NH}_2}$$

(b) Chymotrypsin cleaves a peptide chain at the carboxyl groups of the aromatic amino acids phenylalanine (Phe), tyrosin (Tyr) and tryptophan (typ). Therefore, chymotrypsin cleaves the chain at the following points (shown by arrow) to yield three (I–III) peptides:

$$\text{Leu – Gly – Ser – Met – Phe} \downarrow \text{Pro – Tyr} \downarrow \text{Gly – Val} \xrightarrow{\text{Chymotrypsin}}$$

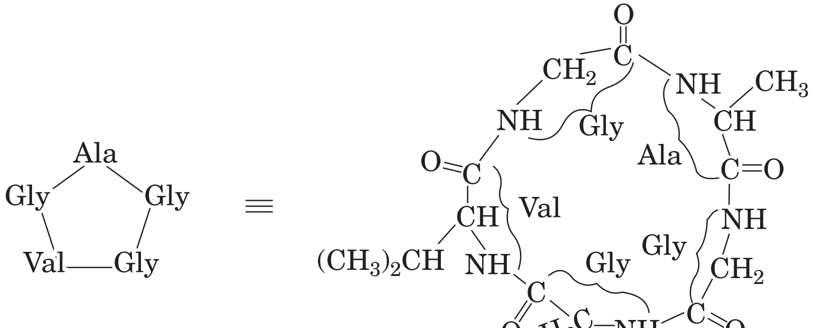
$$\underset{\text{I}}{\text{Leu – Gly – Ser – Met – Phe}} + \underset{\text{II}}{\text{Pro – Tyr}} + \underset{\text{III}}{\text{Gly – Val}}$$

5. A pentapeptide (I) does not release nitrogen upon treatment with HNO_2. On acid-catalyzed hydrolysis, it produces glycine (3 moles), alanine (1 mole) and Valine (1 mole). Its partial hydrolysis gives two dipeptides Ala – Gly and Gly–Ala. Predict the possible structures of the pentapeptide that fit these data; give plausible explanations.

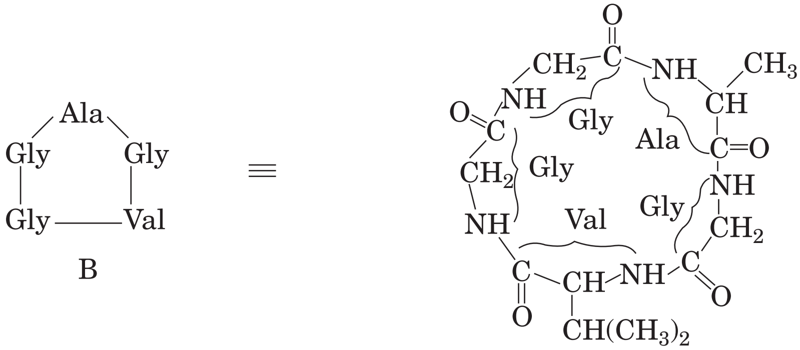
Solution Since the pentapeptide (I) does not release nitrogen upon treatment with HNO_2 ($NaNO_2$/HCl), there is no free —NH_2 group at the N-terminal, and the peptide I must be a cyclic one. On partial acidic hydrolysis, I yields two dipeptides Ala – Gly and Gly – Ala. This suggests that I must contain Gly – Ala – Gly system.

$$\begin{array}{l} \text{Gly – Ala} \\ \qquad\ \ \text{Ala – Gly} \\ \hline \text{Gly – Ala – Gly} \end{array}$$

The remaining two amino acids Val and Gly may exist as Val – Gly or Gly – Val. When these two dipeptide fragments are joined with the tripeptide fragment we may get two possible structures (A and B) of I. These may be shown as follows:



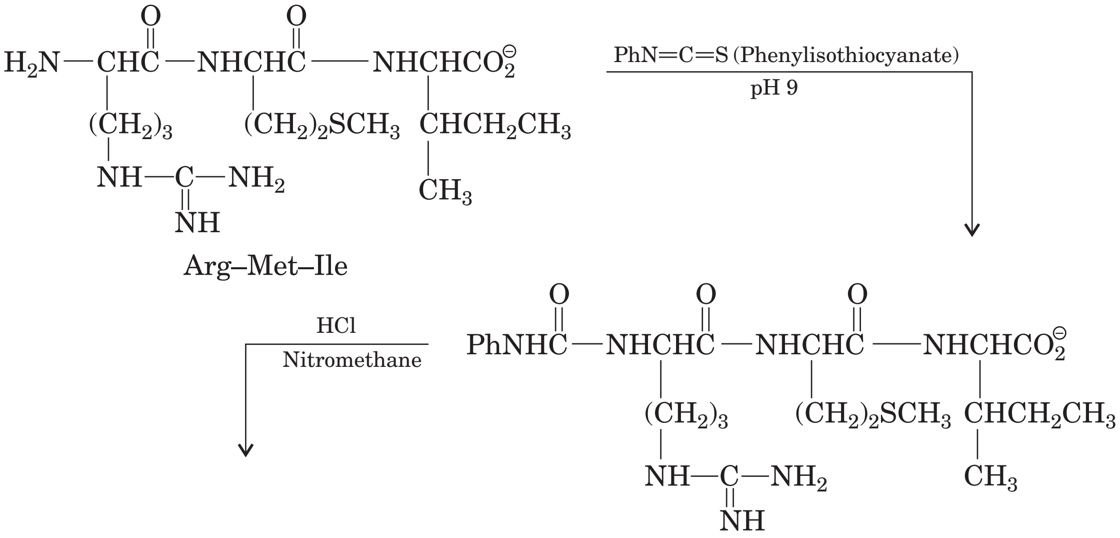
A



B

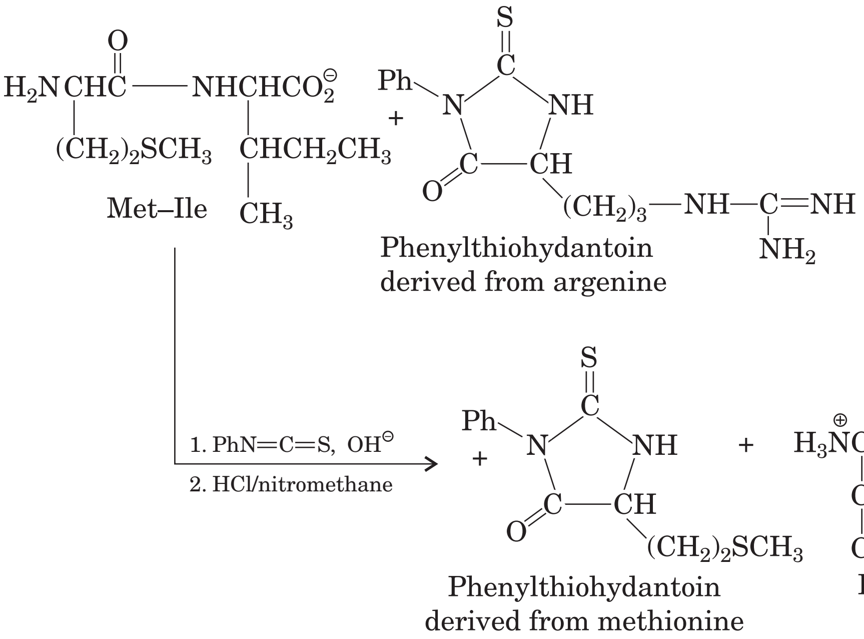
6. Write down the reactions involved in a sequential Edman degradation of the tripeptide Arg – Met – Ile.

Solution

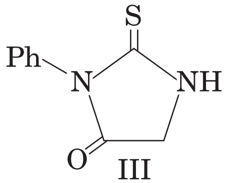


Arg–Met–Ile

$H_2N-\underset{(CH_2)_3NHC(=NH)NH_2}{CH}\overset{O}{\overset{\|}{C}}-NH\underset{(CH_2)_2SCH_3}{CH}\overset{O}{\overset{\|}{C}}-NH\underset{CH(CH_3)CH_2CH_3}{CH}CO_2^{\ominus} \xrightarrow[\text{pH 9}]{\text{PhN=C=S (Phenylisothiocyanate)}} PhNH\overset{O}{\overset{\|}{C}}-NH\underset{(CH_2)_3NHC(=NH)NH_2}{CH}\overset{O}{\overset{\|}{C}}-NH\underset{(CH_2)_2SCH_3}{CH}\overset{O}{\overset{\|}{C}}-NH\underset{CH(CH_3)CH_2CH_3}{CH}CO_2^{\ominus} \xrightarrow[\text{Nitromethane}]{\text{HCl}}$



7. A hexapeptide (I) on complete hydrolysis in the presence of aqueous acid give Arg, Phe, Lys, Gly, Val, Tyr and NH_3 (one equivalent each). Incubation of I with the enzyme chymotripsin yields the dipeptide Arg – Tyr and a tetrapeptide (II) containing Gly, Lys, Phe and Val. When I and II is incubated with carboxypeptidase, there occurs no cleavage. When II is hydrolyzed partially in the presence of acid, Phe – Val, Gly – Lys, Lys – Phe and NH_3 are obtained. However, when II is subjected to a single Edman degradation, the following phenylthiohydantoin III is obtained. Provide a structure for I.



III

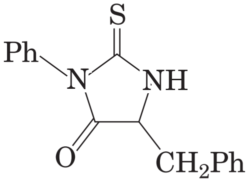
Solution The phenylthiohydantoin III is derived from the amino acid glycine. Therefore, the N-terminal residue in the tetrapeptide II is Gly. Writing Gly first and matching the overlapping regions of the dipeptide fragments we get the structure of II as Gly – Lys – Phe – Val

Gly – Lys
Lys –Phe
Phe – Val

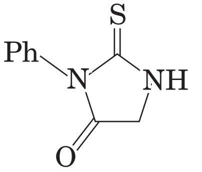
Gly – Lys – Phe – Val

Since II does not undergo hydrolytic cleavage of the C-terminal peptide bond by carboxypeptidase, it must present as an amide. This is also supported by the fact that the hexapeptide I on complete hydrolysis yields ammonia. The formation of Arg – Tyr by the cleavage of the carboxyl peptide bond of Tyr with chymotrypsin suggests that Tyr is bonded to Gly of II. Hence, the structure of the hexapeptide I is Arg – Tyr – Gly – Lys – Phe – Val · NH_2.

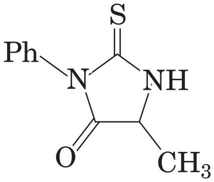
8. **Amino acid analysis of a pentapeptide shows that it contains one Gly, one Ala, one Met and two Phe residues. Treatment of the pentapeptide with carboxypeptidase gives phenylalanine as the first free amino acid released. Sequential treatment of the pentapeptide with phenyl isothiocynate (PITC) followed by mild hydrolysis gives the following derivatives:**



(first time)



(second time)



(third time)

Propose a structure of the starting pentapeptide.

Solution Since carboxypeptide releases phenylalanine, therefore, Phe is the C-terminal amino acid of the pentapeptide. The Edman's reagent releases PTH – Phe as the first derivative, PTH – Gly as the second derivative and PTh – Ala as the third derivative. Therefore, from N-terminal the sequence is Phe – Gly – Ala. It thus follows that the amino acid residue Met must be placed between Ala and Phe. The structure of the pentapeptide may, therefore, be written as follows:

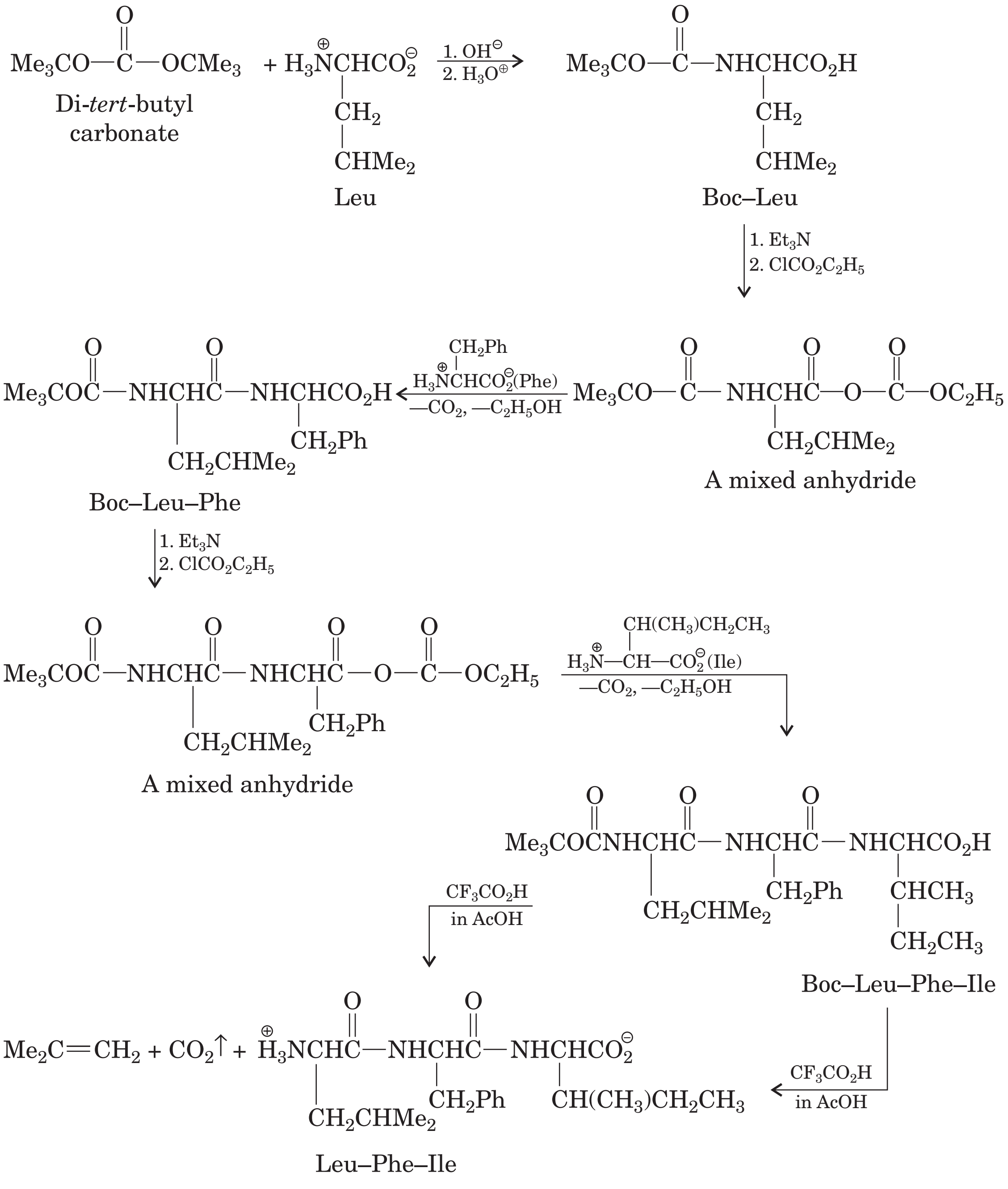
Phe – Gly – Ala – Met – Phe

9. **Show the steps and the intermediates in the synthesis of Leu – Phe – Ile by (a) solution-phase process and (b) solid-phase process.**

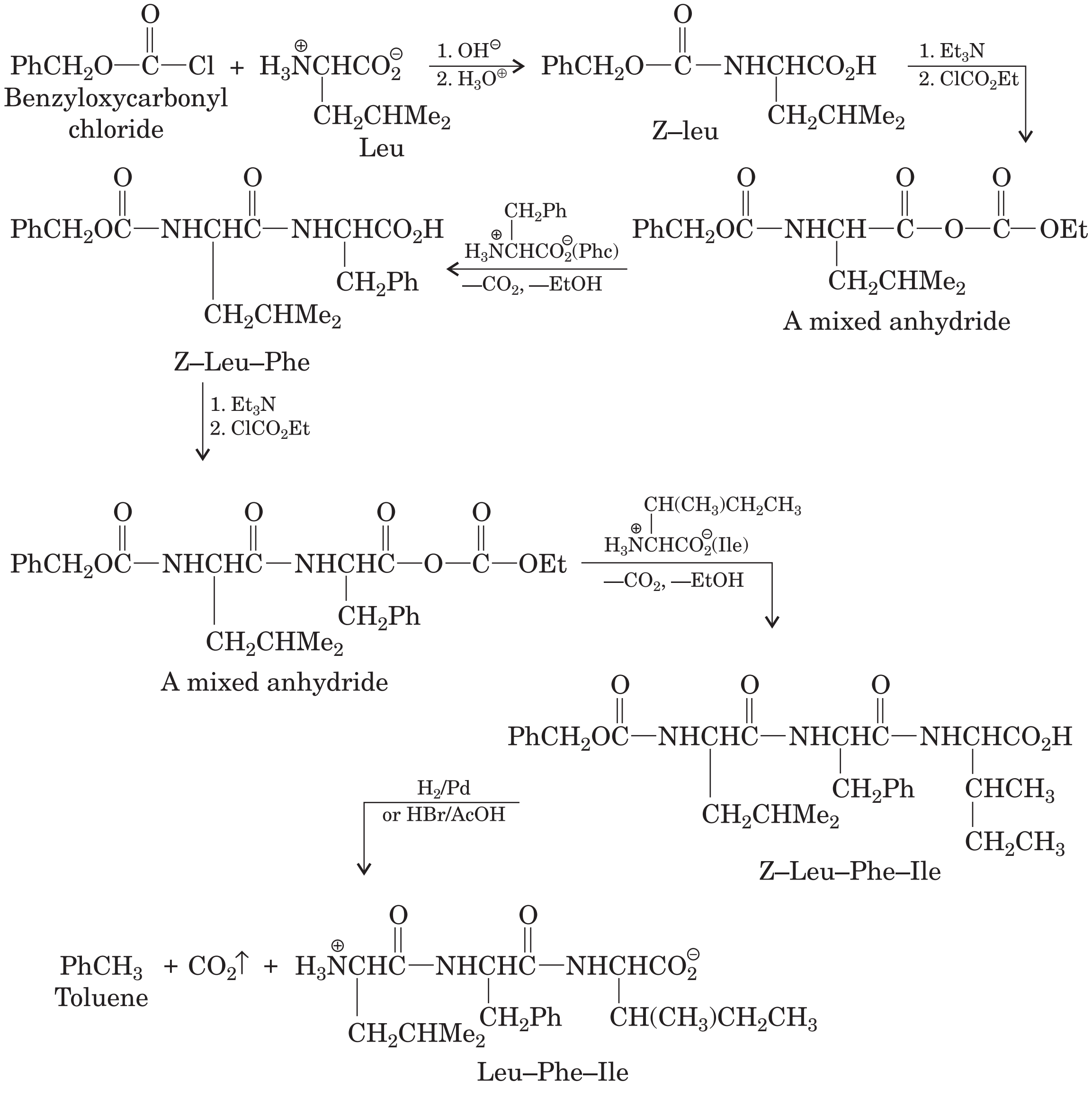
Solution

(a) Solution-phase process

(i) *tert*-Butyloxycarbonyl method

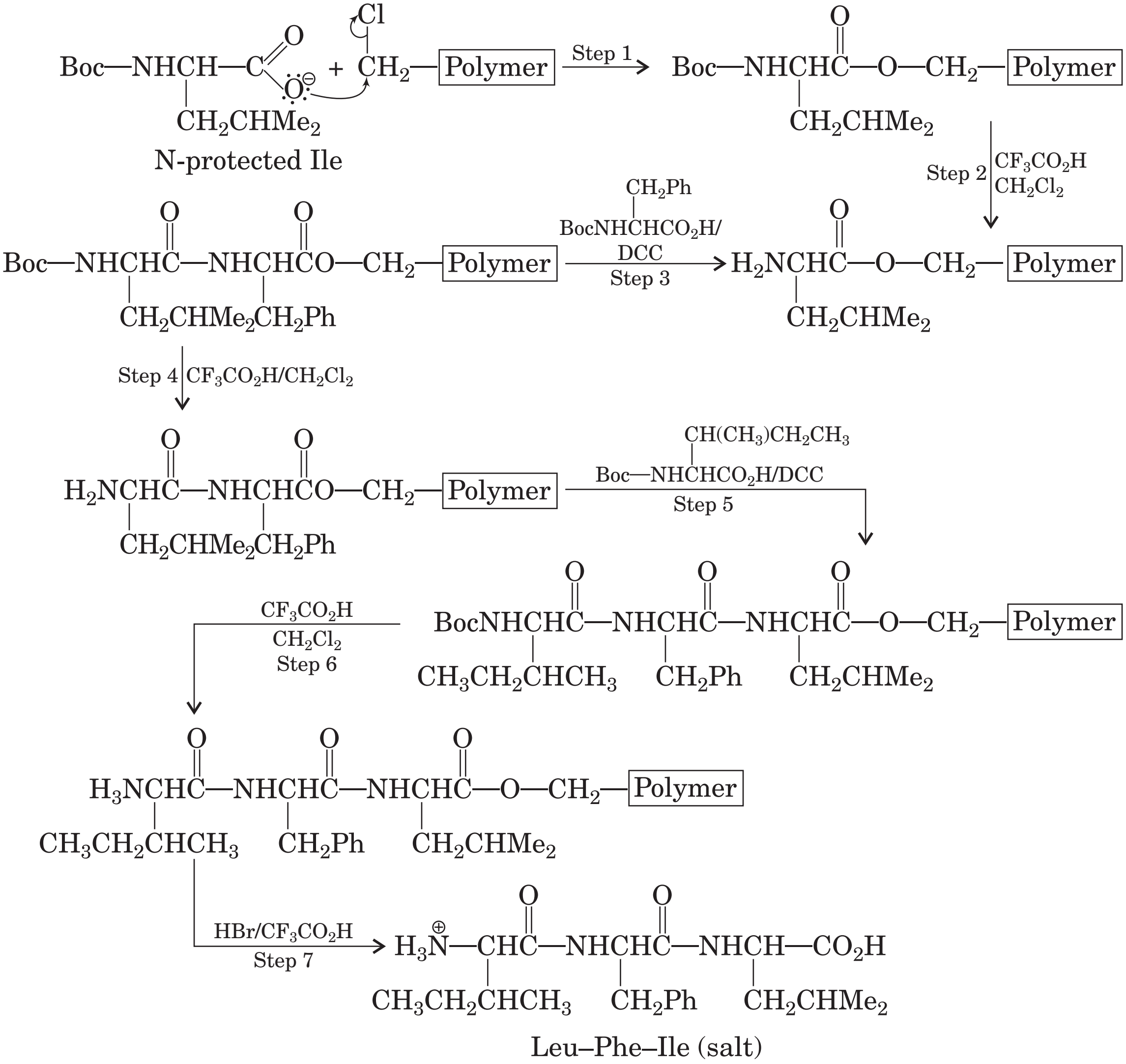


(ii) Benzyloxycarbonyl method:

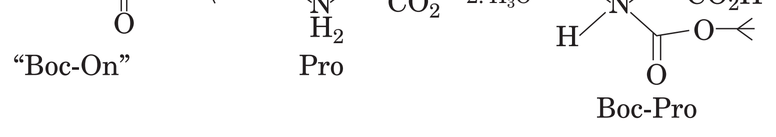


(b) Solid-phase process

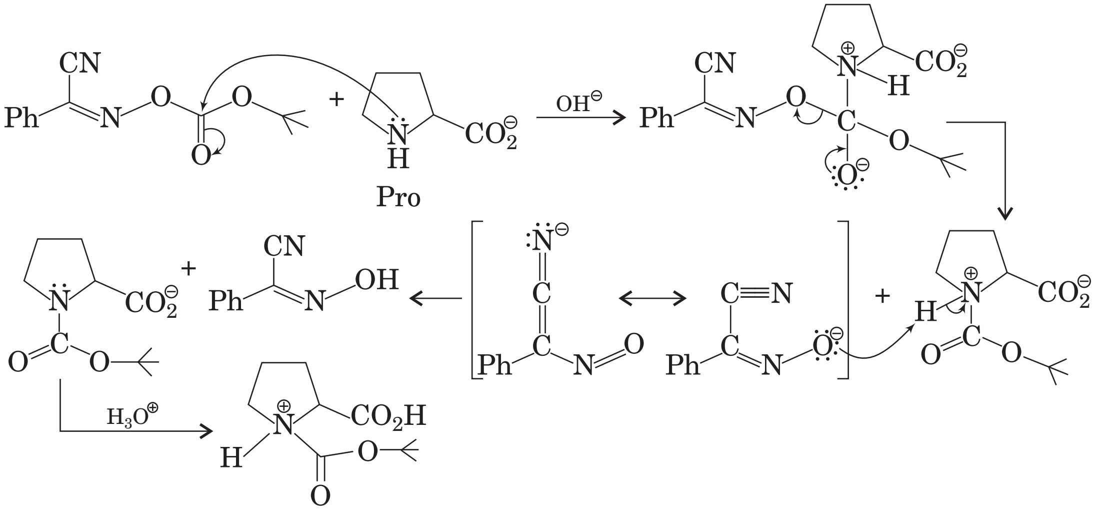
The synthesis of Leu – Phe – Ile by the solid-phase method of Merrifield may be outlined as follows:


Boc—NHCH—C(=O)O⁻ + Cl–CH₂—Polymer
CH₂CHMe₂
N-protected Ile
Step 1
Boc—NHCHC(=O)—O—CH₂—Polymer
Step 2
CF₃CO₂H
CH₂Cl₂
H₂NCHC(=O)—O—CH₂—Polymer
CH₂Ph
BocNHCHCO₂H/
DCC
Step 3
Boc—NHCHC(=O)—NHCHC(=O)O—CH₂—Polymer
CH₂CHMe₂ CH₂Ph
Step 4
CF₃CO₂H/CH₂Cl₂
H₂NCHC(=O)—NHCHC(=O)O—CH₂—Polymer
CH(CH₃)CH₂CH₃
Boc—NHCHCO₂H/DCC
Step 5
BocNHCHC(=O)—NHCHC(=O)—NHCHC(=O)—O—CH₂—Polymer
CH₃CH₂CHCH₃ CH₂Ph CH₂CHMe₂
CF₃CO₂H
CH₂Cl₂
Step 6
H₃NCHC(=O)—NHCHC(=O)—NHCHC(=O)—O—CH₂—Polymer
HBr/CF₃CO₂H
Step 7
H₃N⁺—CHC(=O)—NHCHC(=O)—NHCH—CO₂H
Leu–Phe–Ile (salt)

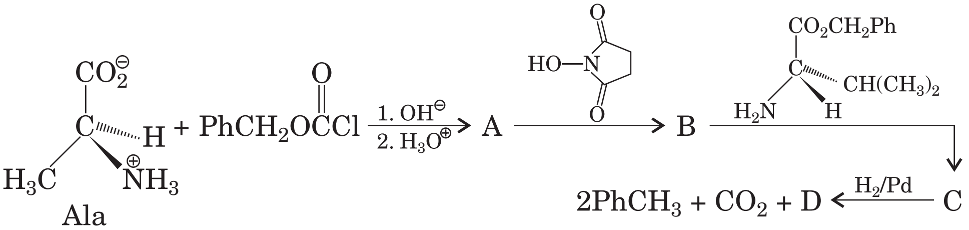
10. When an amino acid is treated with *tert*-butoxycarbonyloximinophenylacetonitrile (“Boc-On”), a Boc-protected amino acid is obtained. Suggest a mechanism for the following reaction.



Solution The mechanism of the reaction involves the steps as follows:



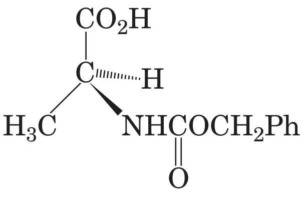
11. Identify the compounds A–D in the following reaction sequence:



In the second step, the carboxyl group is activated by converting it to an *N-hydroxysuccinimide ester*. Explain why this ester is relatively more reactive than methyl or ethyl ester.

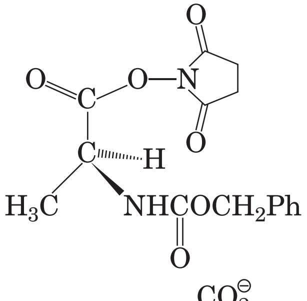
Solution

A =

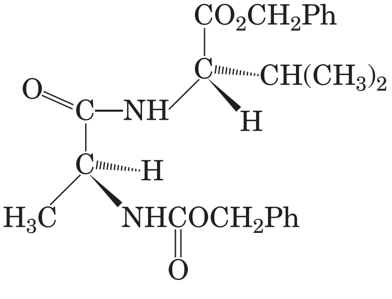


;

B =

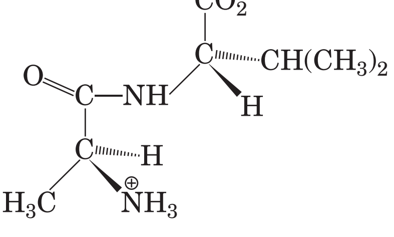


C =

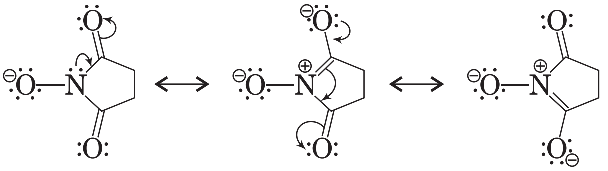


;

D =



The *N*-hydroxysuccinimide ester is relatively more reactive than methyl or ethyl ester because the *N*-hydroxysuccinimide anion is a better (less basic and more stable) leaving group than methoxide or ethoxide ion.



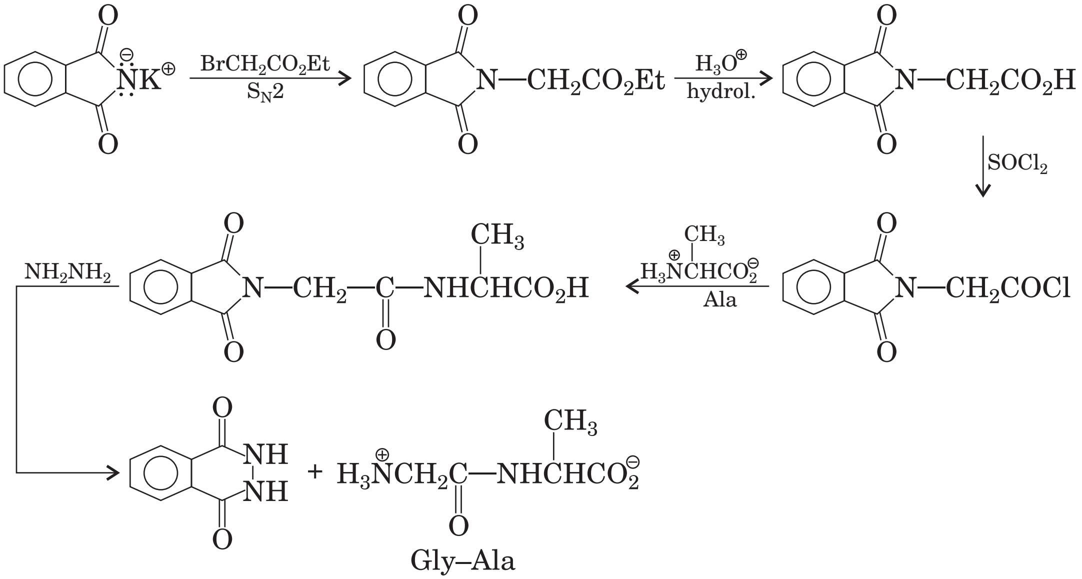
N-Oxysuccinimide anion

(the negative charge on anionic oxygen is stabilized by the –I effect of the adjacent positively polarized N atom)

12. **How would you prepare Gly–Ala and Ala–Gly by using potassium phthalimide and an appropriate bromoester? Which dipeptide is expected to be obtained in large amount?**

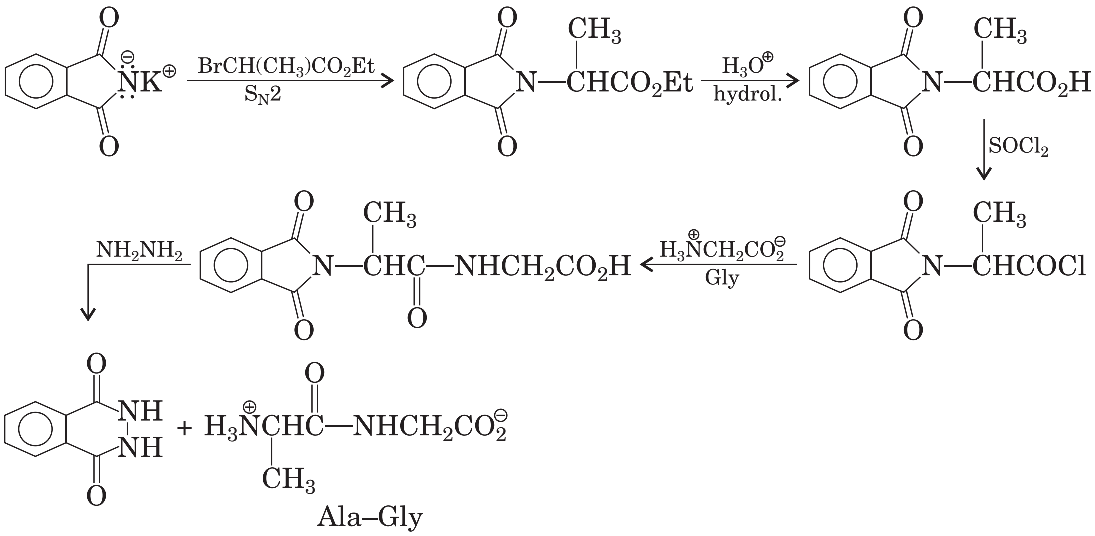
Solution

Preparation of Gly – Ala:



Gly–Ala

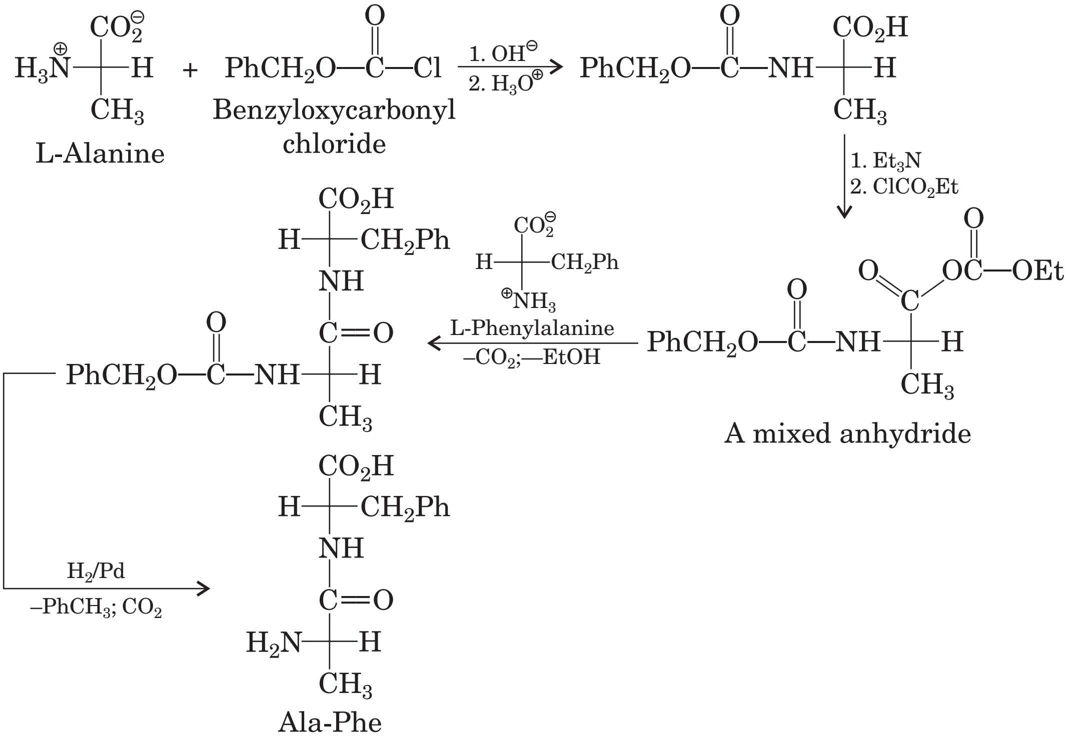
Preparation of Ala – Gly:



Gly – Ala is expected to be obtained in larger amount because the first step of its synthesis (an S_N2 reaction) involves a primary substrate, whereas the first step of the synthesis of Ala – Gly involves a secondary substrate (sterically more hindered towards S_N2 attack).

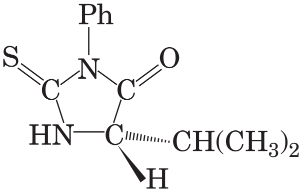
13. Outline the steps in the preparation of Ala – Phe from L-amino acids using bezoyloxycarbonyl (Z-) group as a protecting group.

Solution



14. Draw the structure of the phenylthiohydantoin derivative of L-valine.

Solution The structure of the PTH – Val obtained from the L-amino acid is as follows:



15. Using abbreviated names, write all possible formulations of tripeptide consisting of glycine, valine and phenylalanine.

Solution Each amino acid can function as *N*-terminal residue as well as C-terminal residue. Therefore, six tripeptides are possible and these are

(i) Gly – Val – Phe (ii) Val – Gly – Phe (iii) Phe – Gly – Val
(iv) Gly – Phe – Val (v) Val – Phe – Gly (vi) Phe – Val – Gly

16. Predict the products expected from (a) partial and (b) complete hydrolysis of the tetrapeptide Phe – Gly – Ala – Val.

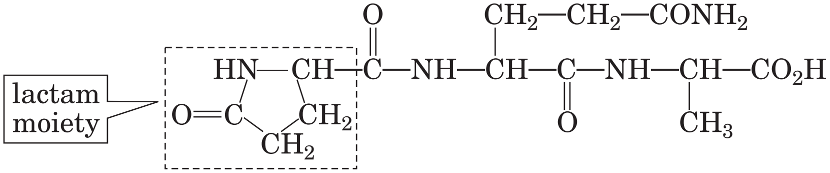
Solution

(a) The dipeptides and tripeptides obtained on partial hydrolysis of Phe – Gly – Ala – Val are as follows:
dipeptides: Phe – Gly, Gly – Ala and Ala – Val
tripeptides: Phe – Gly – Ala and Gly – Ala – Val

(b) On complete hydrolysis the tetrapeptide produces the four component amino acids which are: Phe, Gly, Ala and Val.

17. A tripeptide (A) undergoes complete hydrolysis to yield Glu (2 equiv.), Ala (1 equiv.) and NH_3 (1 equiv.). A contains only one —COOH group and is unable to react with 2,4-dinitrofluorobenzene. When A is incubated with *carboxypeptidase*, Ala is released first. Suggest a reasonable structure for A. [C.U. 2011]

Solution Since *carboxypeptidase* releases Ala as the first amino acid residue, the C-terminal amino acid of A is Ala and therefore, the amino acid sequence is Glu – Glu – Ala. A does not react with the Sanger reagent. This indicates that the H_2N – group of Glu forms a lactam with the —COOH group of the side chain. Since one equivalent of NH_3 is obtained, the —CO_2H group of the side chain of other Glu must exist as —$CONH_2$ group. Hence, the structure of the tripeptide (A) is as follows.



A

18. (a) **Suggest a mechanism for oxidation of a thiol (e.g., C_2H_5SH) to a disulfide (e.g., diethyl disulfide)**

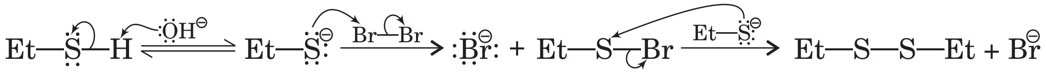
$$2C_2H_5SH \xrightarrow[\text{(mild oxidation)}]{Br_2 \text{ in basic solution}} C_2H_5\text{—}S\text{—}S\text{—}C_2H_5$$

Ethanethiol Diethyl disulfide

(b) **Comment on the unique role of cysteine and cysteine in protein structure.**

Solution

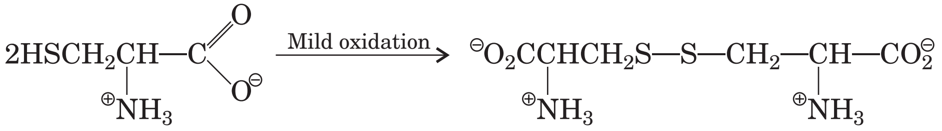
(a) The mechanistic steps involved in oxidation of a thiol to a disulfide are as follows:



Diethyl disulfide

Since the reaction is reversible in nature, a mild reduction cleaves a disulfide to a thiol.

(b) The amino acid cysteine contains a thiol group in its side chain. Two cysteine molecules, therefore, can be oxidized to a disulfide. This disulfide is called cystine.

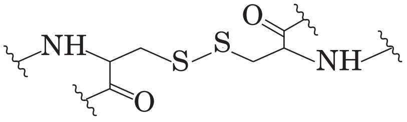
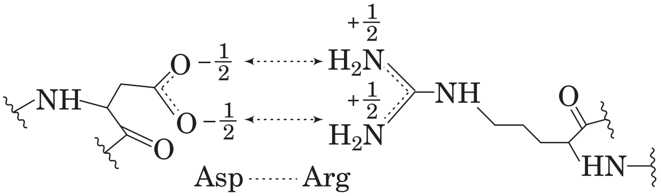
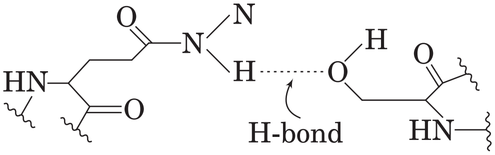
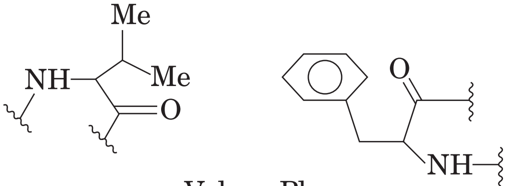


Cysteine Cystine

The two cysteine residues in a protein can undergo oxidation to yield a disulfide. This is what is called a *disulfide bridge* (also called *disulfide linkage*). Disulfide bridges are the only covalent bonds that can form between two nonadjacent amino acids. They can join two chains or link a single chain into a ring. Therefore, they contribute to the overall shape of a fragment by holding the cysteine residues in close proximity.

19. **Show the covalent and noncovalent interactions between the amino acid side chains in proteins with suitable examples.**

Solution Four types of interactions are involved between the amino acid side chains in proteins.

Type of interaction	Example
1. S–S bond between two cysteins (disulfide bridge)	 Cys S—S Cys
2. Electrostatic attraction between oppositely charged ions (salt bridge)	 NH O $-\frac{1}{2}$ O $-\frac{1}{2}$ O $+\frac{1}{2}$ H_2N $+\frac{1}{2}$ H_2N NH O HN Asp……Arg
3. Positively polarized H of O—H and N—H group interacts with an electronegative atom (O or N), i.e., hydrogen bond.	 Gln……Ser
4. Instantaneous dipole-induced dipole attractions (van der Waals interactions)	 Val……Phe

STUDY PROBLEMS

1. How can you determine the C-terminal and N-terminal residue of a peptide chain? **[C.U. 2012, 2014, 2015]**

[**Hint:** See **article no. 10.2.6** (Terminal residue analysis)]

2. Outline briefly the chemical strategy for the synthesis of the tripeptide Ala – Gly – Val following the Merrified solid phase synthetic method. **[C.U. 2014]**

[**Hint:** See **article no. 10.2.7.2 (solid phase peptide synthesis)**]

3. Delineate the pathway to synthesize the dipeptide Val – Gly using direct synthetic method involving DCC. **[C.U. 2015]**

[**Hint:** Z-protected valine is to be treated with glycine benzyl ester and finally deprotection is carried out by treating with H_2/Pd. See **article no. 10.2.7.1** (peptide synthesis using DCC).]

4. Write down the complete structures for the following peptides and indicate whether each peptide is acidic, basic or neutral.

(a) Ala – Gly – Cys (b) Gly – Ala – Phe

(c) Arginylleucylglycine (d) Threonylmethionine

5. *Gramicidin S* (a polypeptide having antibiotic properties) on partial hydrolysis yields the following di- and tripeptides.

Leu – Phe ; Phe – Pro ; Orn – Leu ; Val – Orn ; Phe – Pro – Val ; Val – Orn – Leu ; Pro – Val – Orn.

Predict the structure of *gramicidin S*.

6. A tripeptide on hydrolysis produces two molecules of alanine and one molecule of phenylalanine. Give the possible structures of the tripeptide.

7. Write down a scheme for the synthesis of the dipeptide, Gly – Ala, using DCC promoted peptide bond formation. Give the mechanism. **[C.U. 2011, 2013]**

[**Hint:** See **article no. 10.2.7** (use of DCC).]

8. How would you synthesize the tripeptide Phe – Gly – Ala applying the Merrifield methodology and using Boc-group as the N-protecting group. What are the advantages associated with the solid-phase peptide synthesis. **[C.U. 2012]**

[**Hint:** See the **solved problem 9.**]

9. How would you differentiate chemically between the following peptides?

Gly – Ala – Ala and Ala – Gly – Ala

[**Hint:** Treatment with HNO_2 follow by iodoform reaction can be used to differentiate between these two tripeptides.]

10. A tripeptide having the empirical composition (Phe, Gly, Ser) is subjected to the action of *carboxypeptidase*. The first free amino acid to appear in solution is Phe. When the tripeptide is subjected to Edman degradation, the phenylthiohydantoin derivative of glycine is obtained. Deduce the structure of the tripeptide and write the steps involved in Edman degradation. **[C.U. 2010]**

11. Synthesize the dipeptide L-alanyl-L-phenylalanine using suitable protecting groups.

12. How is the —NH_2 group of an amino acid protected by its Boc derivative during peptide synthesis? Also, mention its removal in the subsequent steps.

13. Explain with mechanism the role of 2,4-DNFB for the determination of N-terminal residue of a protein.

14. Explain why the benzoyl group cannot be used as an N-protecting group for peptide synthesis.

15. What are the principal forces maintaining the secondary structure of proteins. **[C.U. 2010]**

16. Illustrate an application of 2,4-dinitrofluorobenzene in structure determination of peptides. How would you justify its choice over the much less expensive 2,4-dinitrochlorobenzene?

17. Explain why the peptide C—N bond is stronger and shorter than the usual C—N single bond and why the rotation is restricted about this bond.

18. Outline a chemical method for determination of C-terminal amino acid of a protein.

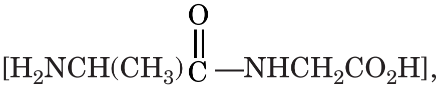
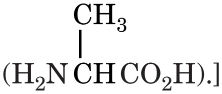
19. Propose a mechanism for the coupling of acetic acid and aniline using DCC as a coupling agent.

20. Show how you would synthesize Leu – Gly – Ala – Val – Phe starting with Boc – Ala – Val –Phe – $\boxed{\text{Polymer}}$.

21. What is Merrifield resin? How can it be used to prepare Gly – Phe. Why cannot the amino protection be done by benzoyloxycarbonyl group in this process except in the last step?

[**Hint:** The N-protection cannot be done by Boc-group because its removal (by H_2/Pd or HBr/AcOH) may cause cleavage of the bond between the polymer and the peptide chain. It can be used in the last step (i.e., for the protection of the last amino acid) because after the introduction of the last amino acid residue the peptide is to be detached from the polymer.]

22. A dipeptide on hydrolysis gives two amino acids X and Z. If the dipeptide is first treated with HNO_2 and then hydrolysis is carried out, X and lactic acid are obtained. X on heating produces 2,5-diketopiperazine. Identify X and Z and write the structure of the dipeptide. **[C.U. 2010]**

[**Hint:** The dipeptide is Aly – Gly [ $H_2NCH(CH_3)\overset{\overset{\large O}{\|}}{C}—NHCH_2CO_2H$], X is glycine ($H_2NCH_2CO_2H$) and Z is alanine ( $H_2N\overset{\overset{\large CH_3}{|}}{C}HCO_2H$).]

23. Proline inhibits the formation of a helical conformation comment.

[**Hint:** Proline is a secondary α-amino acid. So, the protein obtained from proline contains no H atom attached to the N atom. For this reason, H-bonding with carbonyl oxygen does not take place and as a result, the formation of a helical conformation is inhibited.]

24. How is Cysteine-Cystine interconversion used to give hair a new shape (i.e., from straight to curly or from curly to straight)?

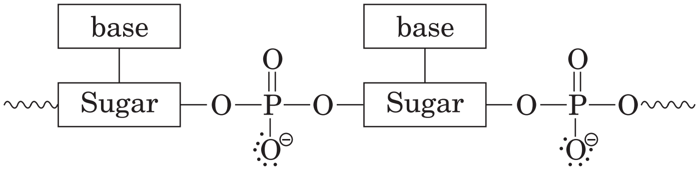
25. If you synthesize the tripeptide Leu – Phe – Ala from amino acids prepared by the strecker synthesis, how many stereoisomers would you expect to be obtained?

26. Discuss the salient features of secondary and tertiary structures of protein molecules. **[C.U. 2012]**

[**Hint:** See **article no. 10.2.9.**]

10.3 NUCLEIC ACIDS

The three major kinds of biopolymers are polysaccharides, proteins, and nucleic acids. Nucleic acids are molecules of definite compositions derived form a sugar unit, a nitrogenous base and a phosphoric acid unit. As they are found to be present in the nuclei of all living cells of animals and since they carry an acidic moiety (phosphate unit), they have been given the generic name nucleic acid. Like proteins, nucleic acids also contain a long chain, i.e., a backbone, which, except for length, is the same in all nucleic acid molecules. Where the backbone of the protein molecule is a polyamide chain (a polypeptide chain), the backbone of the nucleic acid molecule is a polyester chain (called a polynucleotide chain). The ester is derived from phosphoric acid (the acid part) and a sugar (the alcohol part).



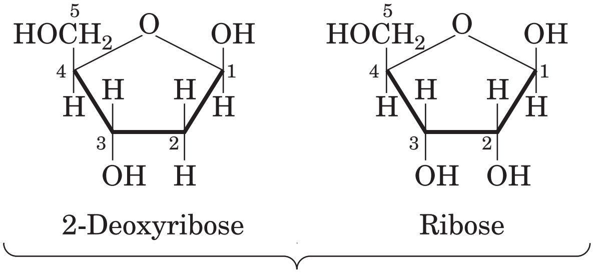
Polynucleotide chain

There are two types of nucleic acids: *deoxoyribonucleic acid* (DNA) and *ribonucleic acid* (RNA). Of all fields of chemistry, the study of the nucleic acids is perhaps the most exciting because these compounds are the substance of heredity. In fact, DNA encodes an organism's entire hereditary information and controls the division of cell and the growth. In almost all organism, the genetic information stored in DNA is transcribed into RNA and subsequently, this information is translated for the synthesis of all proteins required for cellular structure and function.

10.3.1 Structure of Nucleic Acids

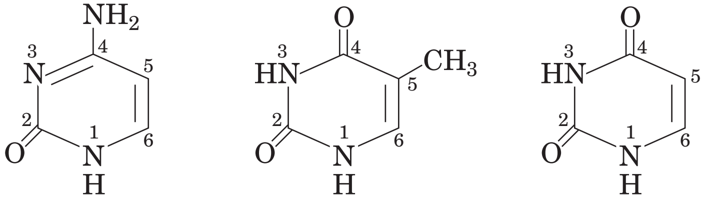
(a) Primary Structure The structures of nucleic acids have been determined by both physical and chemical means. On complete hydrolysis, the nucleic acids afford a mixture containing phosphoric acid, a sugar (ribose or 2-deoxyribose), two purine bases (adenine and guanine), and three pyrimidine bases (uracil, cytosine and thymine).

H_3PO_4
Phosphoric
acid



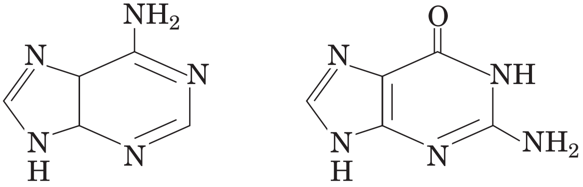
2-Deoxyribose Ribose

Sugars



Cytosine (C) Thymine (T) Uracil (U)

Pyrimidine bases



Adenine (A) Guanine (G)

Purine bases

The difference between DNA and RNA lies in the fact that the sugar obtained from the former is 2-deoxyribose (2-deoxy means that the sugar lacks an —OH group at 2-position), whereas that from the latter is ribose. Both of these sugar units are found in the furanose form and are linked through their β-1-position to 1-position of pyrimidine bases and 9-position of the purine bases. The bases present in DNA are the two purines namely **adenine (A)** and **Guanine (G)** and the two pyrimidines namely **Cytosine (C)** and **thymine (T)**. RNA also contains only four bases. The three bases (adenine, guanine, and cytosine) are the same as those in DNA, but the fourth base in RNA is uracil instead of thymine (thymine is 5-methyluracil). The sugar units are joined to the phosphate through the C-3 and C-5 hydroxyl group.

Nucleotides and Nucleosides

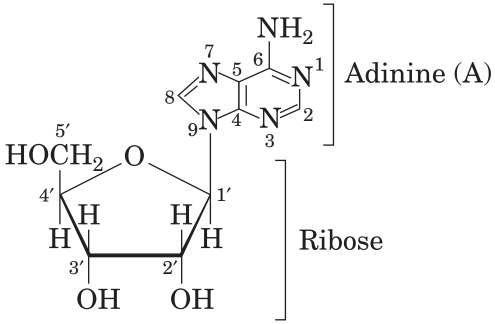
Degradation of nucleic acids under milder conditions results in the formation of relatively simple molecules called *nucleotides* possessing a phosphate unit and a sugar (pentose) unit. On careful hydrolysis, nucleotides eliminate phosphoric acid forming another class of compounds known as *nucleosides*. Thus, a base-sugar phosphoric acid unit is called a nucleotide and a base-sugar unit called a nucleoside. The names of nucleosides and nucleotides are based upon the types of bases present in them. The main structural features and nomenclature of nucleosides and nucleotides of two nucleic acids are shown as follows.

Nucleosides and nucleotides of RNA molecule in which the sugar part is ribose:

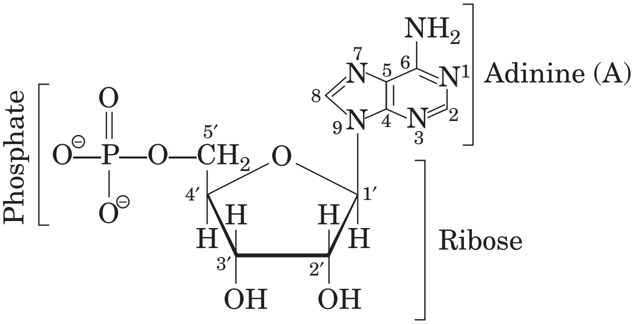
Ribonucleosides

Ribinucleotides

1. **Base : Adenine**

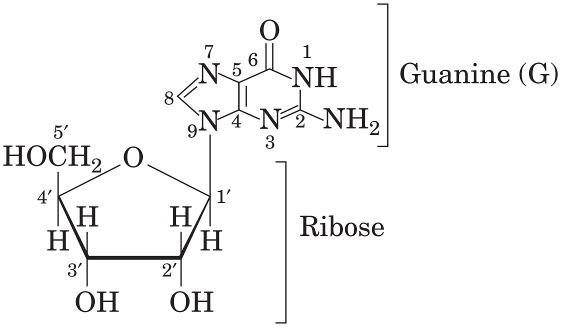


Adenosine

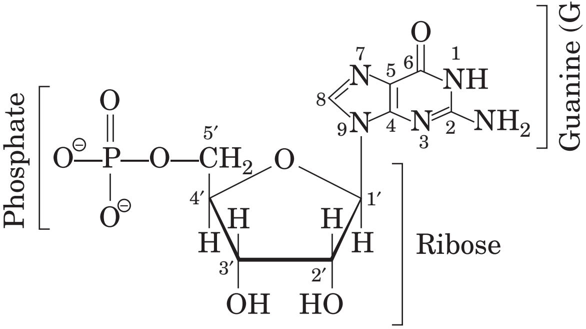


Adenylic acid
or
Adenosine 5′-monophosphate
(Abbreviated name: AMP)

2. **Base : Guanine**

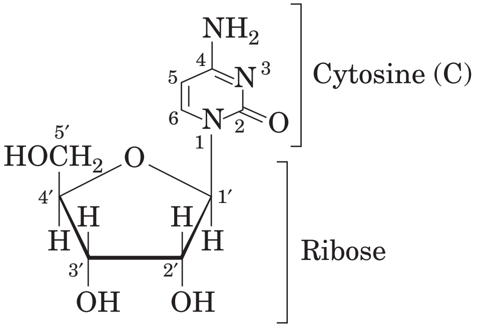


Guanosine

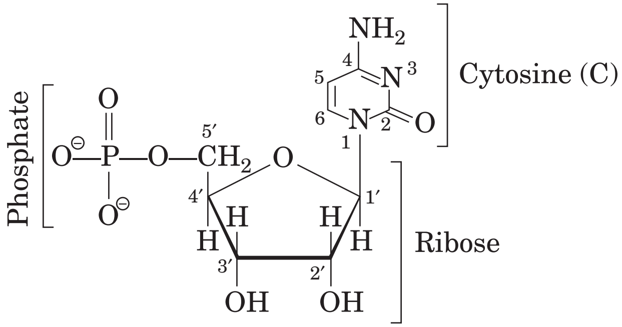


Guanylic acid
or
Guanosine 5′-monophosphate
(Abbreviated name: GMP)

3. **Base : Cytosine**

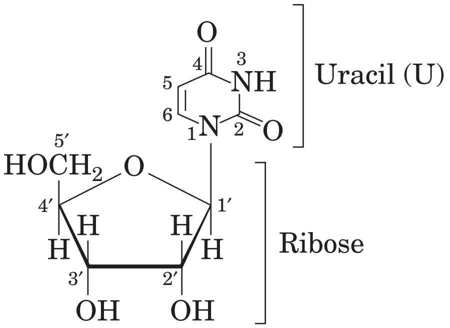


Cytidine

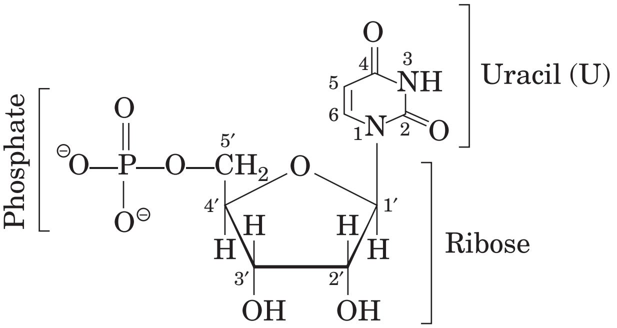


Cytidylic acid
or
Cytidine 5′-monophosphate
(Abbreviated name: CMP)

4. **Base: Uracil**



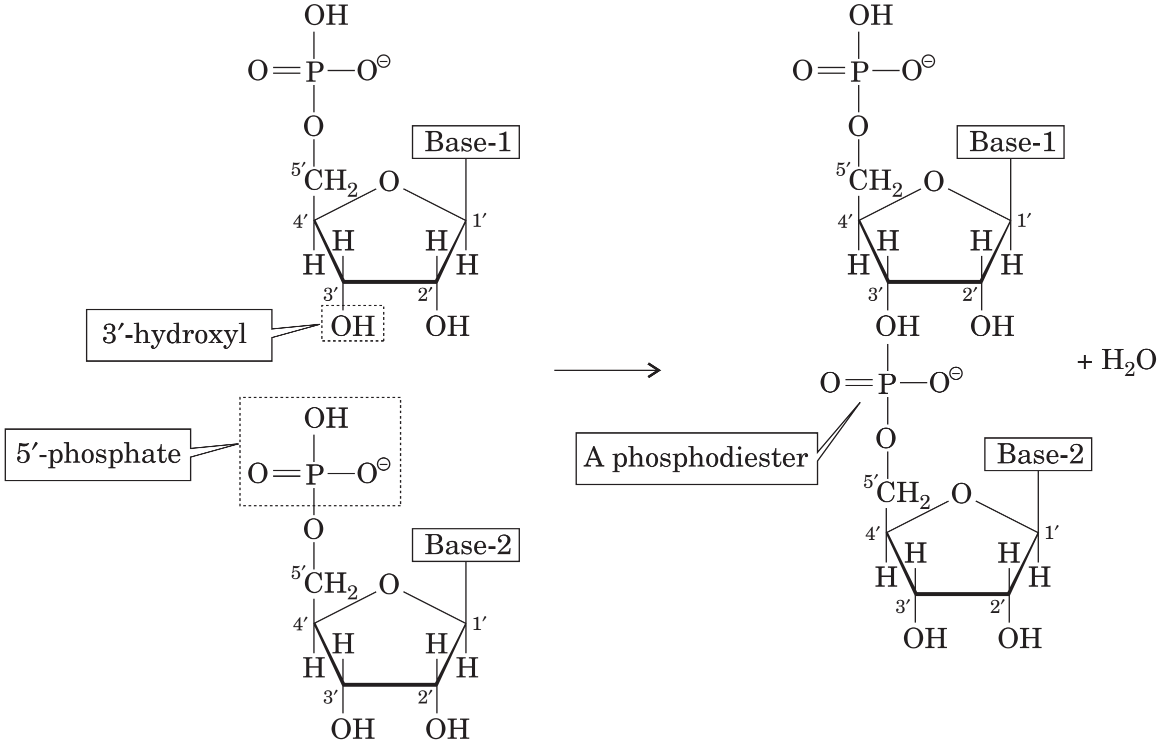
Uridine



Uridylic acid
or
Uridine 5′-monophosphate
(Abbreviated name: UMP)

The structure of ribonucleic acid

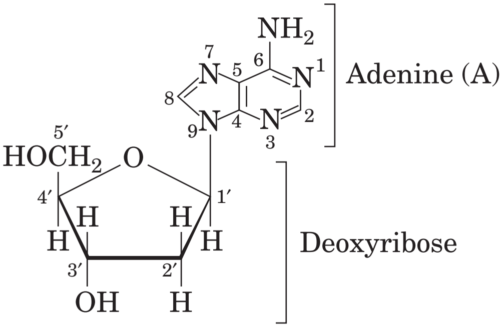
Each nucleotide has a phosphate group on its 5′ carbon (the end carbon of ribose) and a hydroxyl group on the 3′ carbon. Two nucleotides are joined by a phosphate ester, linkage between the 3′-hydroxyl group of one nucleotide and the 5′-phosphate group of another. The RNA polymer (a polynucleotide) consists of many such nucleotides bonded this way, with a phosphate ester linking a 3′end of one nucleotide to the 5′ end of another. Unless an RNA molecule exists in the form of a large ring, it has always two terminals; one terminal has a free 3′ group, and the other terminal has a free 5′ group.



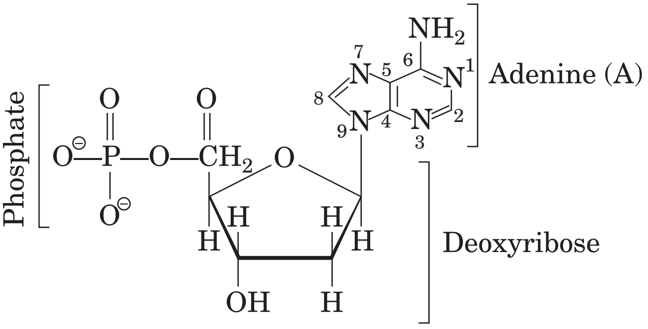
Nucleosides and nucleotides of DNA molecule in which the sugar part is 2-deoxyribose:

Deoxyribonucleosides **Deoxyribonucleotides**

1. Base: Adenine

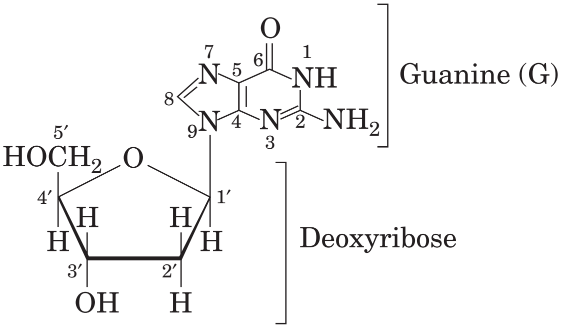


2′-Deoxyadenosine

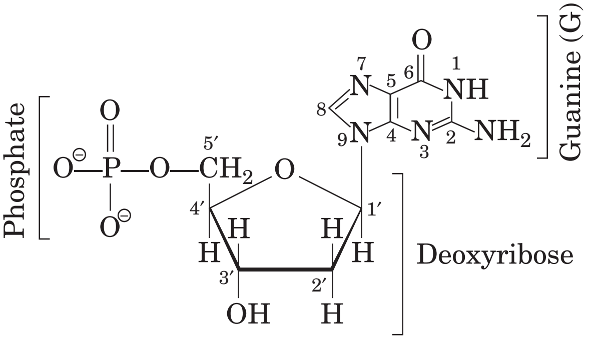


Deoxyadenylic acid
or
2′-Deoxyadenosine-5′-monophosphate (dAMP)

2. Base: Guanine

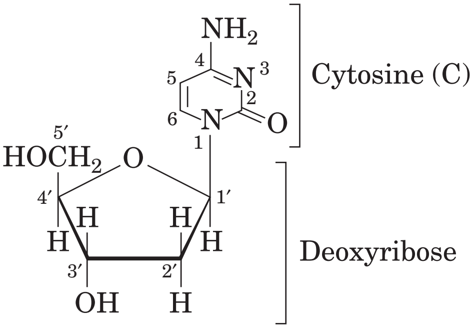


2′-Deoxyguanosine

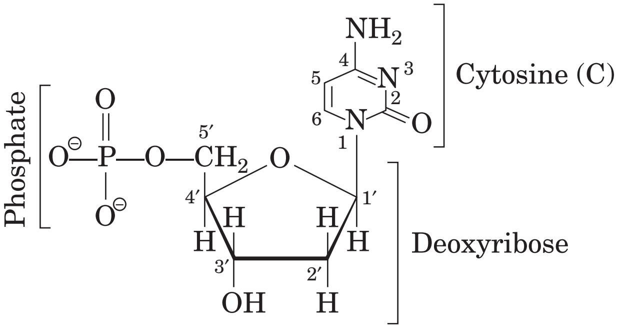


Deoxygunilic acid
or
2′-Deoxyguanosine 5′-monophosphate (dGMP)

3. Base: Cytosin

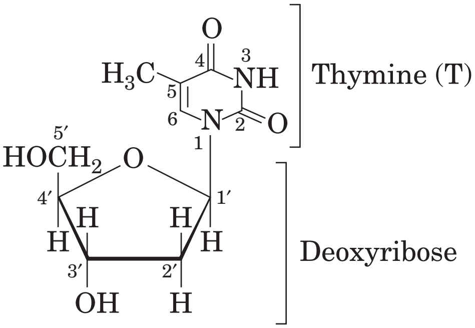


2′-Deoxycytidine

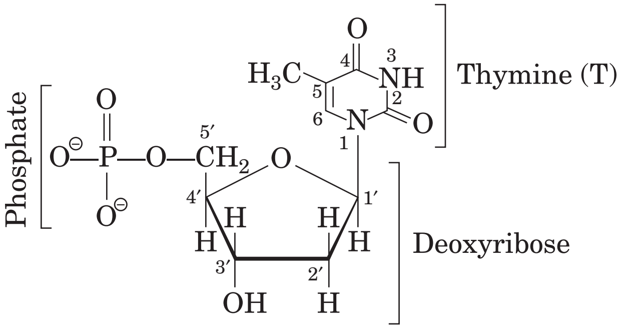


Deoxycytidylic acid
or
2′-Deoxycytidine 5′-monophosphate (dCMP)

4. Base: Thymine



Thymidine



Deoxythymidylic acid
or
Thymidine 5′-monophosphate (dTMP)

The names of the Bases, the Nucleosides and the Nucleotides are given in the following table:

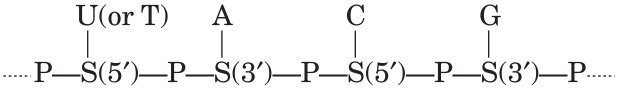
Base	Ribonucleoside	Ribonucleotide	Deoxyribonucleoside	Deoxyribonucleotide
Adenine	Adenosine	Adenosine 5′–monophosphate	2′-Deoxyadenosine	2′-Deoxyadenosine 5′–monophosphate
Guanine	Guanosine	Guanosine 5′–monophosphate	2′-Deoxyguanosine	2′-Deoxyguanosine 5′–monophosphate
Cytosine	Cytidine	Cytidine 5′–monophosphate	2′-Deoxycytidine	2′-Deoxycytidine 5′–monophosphate
Thymine	—	—	Thymidine	Thymidine 5′–monophosphate
Uracil	Uridine	Uridine 5′-monophosphate	—	—

It is to be noted that only thymine containing DNA-nucleoside is named as thymidine as no corresponding RNA-nucloside exists.

The positions of bases (A, G, C and T in DNA and A, G, C and U in RNA) can have different permutations and that lead to the formation of varieties of DNA and RNA molecules, each having specific role to play. Thus, the nucleic acids, though basically similar, differ from each other in number, type and sequence of heterocyclic bases. The manner in which the sugar, phosphate and bases are linked with one another in the nucleic acids is known as the **primary structure of nucleic acid**.

The primary structures of RNA (a part) and DNA (a part) are shown in the following figures (Figure 10.6 and 10.7).

The abbreviated structure of a DNA and RNA molecule (a part) may be represented as follows:



$$\cdots\text{P}—\overset{\substack{\text{U(or T)}\\ |}}{\text{S}}(5')—\text{P}—\overset{\substack{\text{A}\\ |}}{\text{S}}(3')—\text{P}—\overset{\substack{\text{C}\\ |}}{\text{S}}(5')—\text{P}—\overset{\substack{\text{G}\\ |}}{\text{S}}(3')—\text{P}\cdots$$

S = Sugar unit ; P = Phosphate linkage ; U (for RNA), T (for DNA), A, C, G (for both) = Bases.

(b) Secondary structure Quantitative analysis of DNA hydrolysate revealed that in DNA the ratio of adenine to thymine and guanine to cytosine are 1 : 1 even though the base composition in DNA varied from one species to the other. Based upon these observations and assumptions it was proposed that the DNA molecule actually consists of two separate polynucleotide strands leading in opposite directions and coiled about a common axis as right-handed helices. X-ray diffraction studies of DNA provided support for this structure.

The polynucleotide chains of the double helix are held together at definite intervals through hydrogen bonds. Thus, *guanine of one coil is hydrogen bonded, to cytosine of the other*. Similarly, adenine of one coil is hydrogen bonded to thymine of the other. The former pairing involves three hydrogen bonds $(\text{C}\equiv\text{G})$, whereas the latter involves only

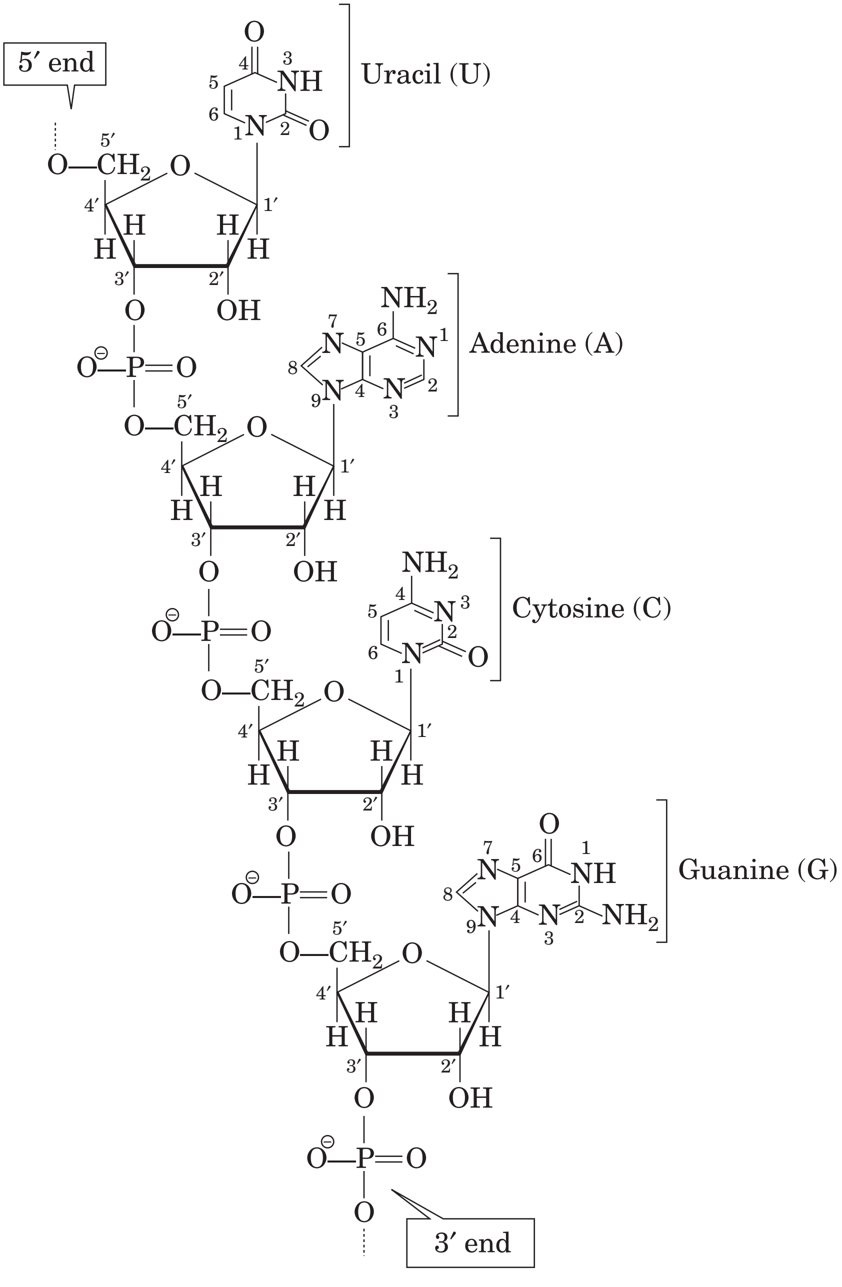


Figure 10.6 Part of an RNA molecule

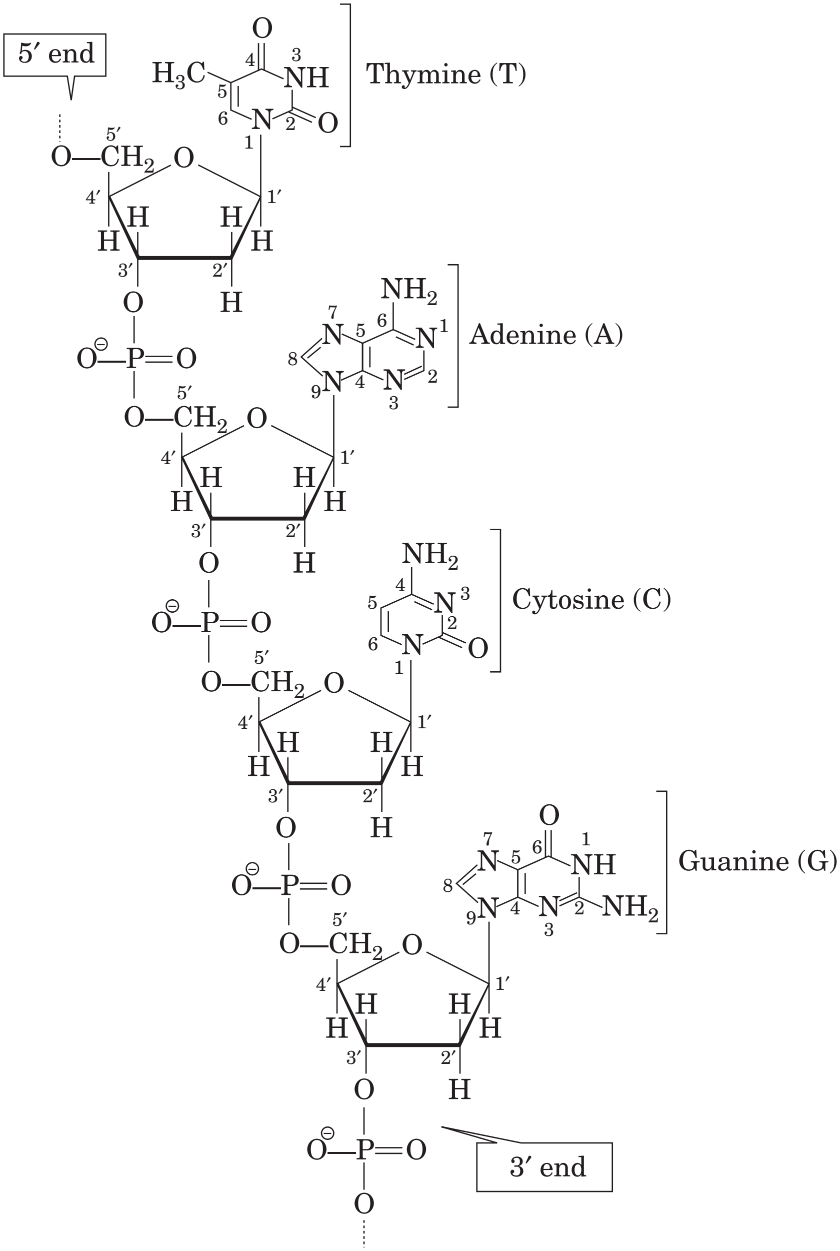
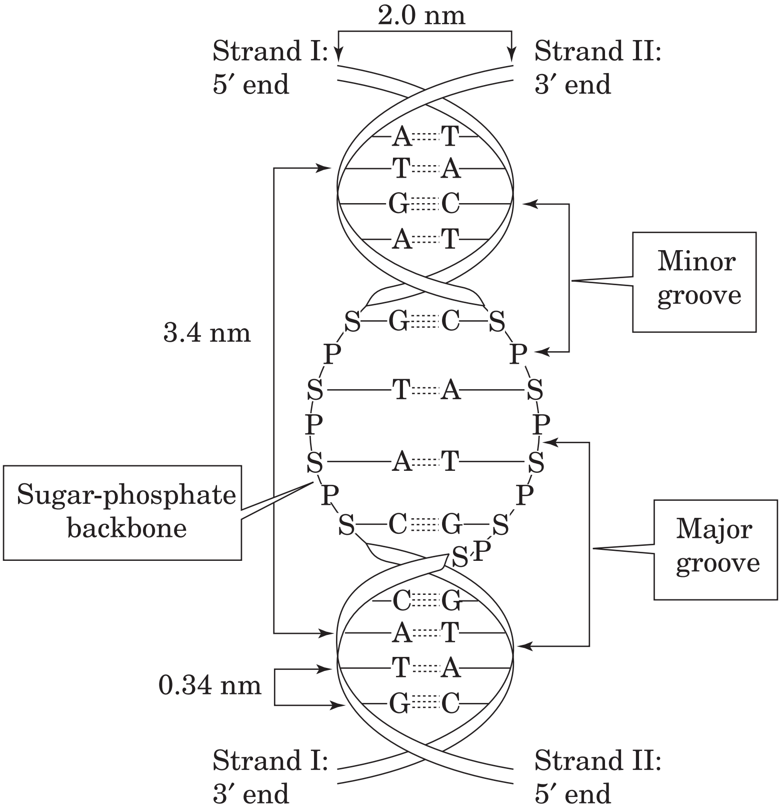


Figure 10.7 Part of a DNA molecule

two (A=T). This is the most stable arrangement as no other pairing of these four bases can lead to such strong bonding. Base pairing does not take place between adenine and cytosine or between thymine and guanine, i.e., base pairing does not take place between purine–purine and pyrimidine–pyrimidine. Using molecular scale model, *Watson* and

Crick have shown that base pairing occurs in a specific way because purine–purine base pairing fails due to their large size which generates steric interactions and pyrimidine–pyrimidine base pairing cannot occur because of electronic and steric reasons (discussed later). The Watson–Crick model not only explained the base equivalence but other important characteristics such as *replication* of DNA. The salient features of Watson–Crick model are summarized as follows.



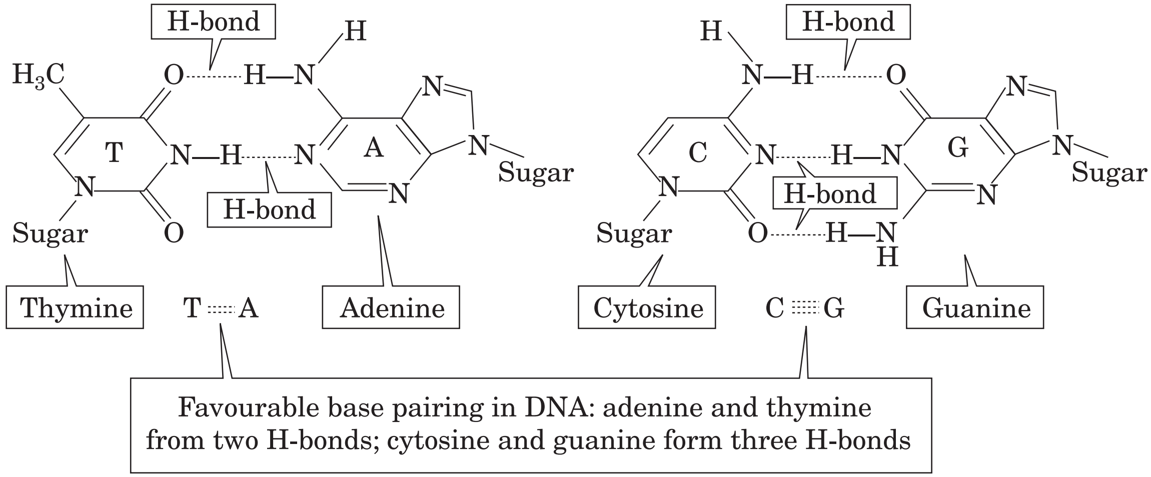
Double helix structure of DNA
(S = Deoxyribose, P = Phosphate, ┈┈ = H-bonds)

(i) The two DNA strands in a α-helical structure run in opposite directions, i.e., from 5′-end to 3′-end in case of one strand and from 3′-end to 5′ end in the other strand. The strand on the right, for example, runs from top (5′) to bottom (3′), whereas the strand on the left runs from bottom (5′) to top (3′). Therefore, 5′ of one strand faces 3′ of the other and *vice-versa*.

(ii) Each strand has a sugar phosphate backbone on the periphery of the helix with bases occurring in the centre. The planes of heterocyclic bases are orthogonal to the axis of the helix. It should be noted that in a DNA molecule the sugar phosphate backbone is completely regular, the sequence of heterocyclic bases can be of many different permutations leading to the formation of different base pairs.

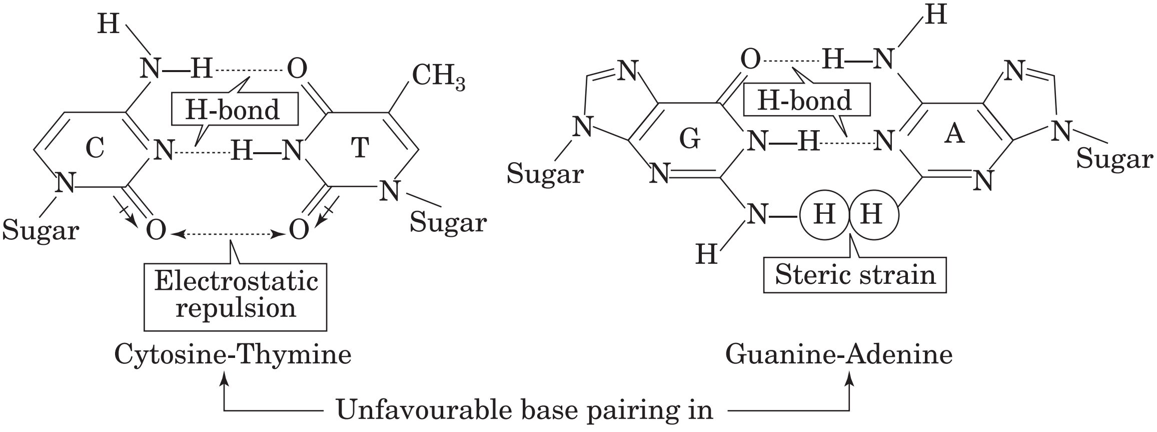
(iii) Since the base pairing always occurs between adenine and thymine and between guanine and cytosine, the base sequence of one strand automatically fixes that of the other, and hence, the two strands of the double helix are complementary and not identical.

The distance between any two adjacent base pairs is 0.34 nm. Also, it has been found that the distance between any two successive turns of the helix is 3.4 nm. This suggests that there are ten base pairs in each turn. The diameter of the helix is about 2.0 nm.



Favourable base pairing in DNA: adenine and thymine from two H-bonds; cytosine and guanine form three H-bonds

The diagrams of other possibilities of base pairing which suffer from steric or electronic destabilization are given below:



Cytosine-Thymine

Guanine-Adenine

Unfavourable base pairing in

The cytosine-thymine pairing suffers from carbonyl dipole repulsion, as well as steric interaction between the two oxygens. The guanidine-adenine pairing, on the other hand, is destabilized by steric strain between the two close H atoms (encircled).

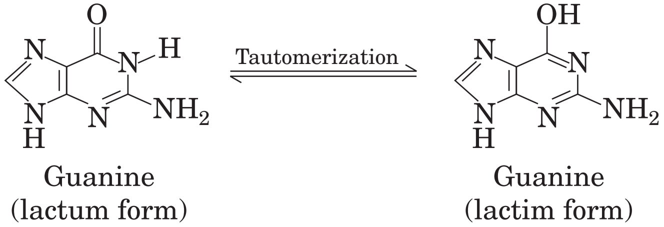
When heated, the two strands of DNA separate from each other. This is what is called *melting*. When cooled these strands again hybridize. This is what is called *annealing*.

The temperature at which the two strands separate completely is called its melting temperature (Tm).

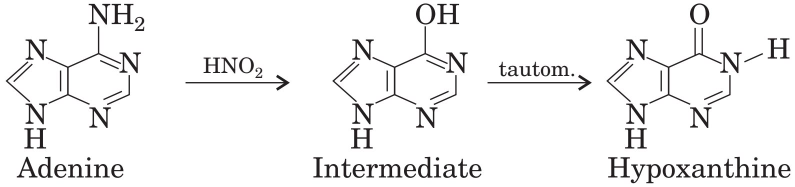
Unlike DNA, RNA has been shown to consist of a single-stranded threadline helix having some intramolecular hydrogen bonding between the heterocyclic bases.

10.3.1.1 Genetic Diseases

Genetic diseases can occur if there takes place any change in normal base pairing caused by some chemical processes within the cell or being influenced by some external agents. Guanine, for example, takes part in DNA molecule in its lactum form and pairs with cytosine. However, if it is transformed into the lactium form by tautomeric change, pairing fails to take place with cytosine, but occurs with thymine. As a result of this, abnormal DNA molecules are generated and that genetic information is transmitted to the daughter cells leading to genetic diseases.



Mutation of DNA molecule can also take place by chemicals (mutagens), like nitrous acid (HNO_2). Heterocyclic bases like adenine, guanine or cytosine containing aromatic —NH_2 group can undergo diazotization by nitrous acid followed by nucleophilic attack by water and loss of N_2 (S_NAr) to yield the corresponding hydroxy compound. This intermediate obtained from adenine then tautomerizes to give hypoxanthine.



10.3.1.2 Points of Difference between DNA and RNA

Deoxyribonucleic acid (DNA)	Ribonucleic acid (RNA)
1. The sugar present in DNA is 2-deoxy-D-ribose	1. The sugar present in RNA is D-ribose
2. Cytosine and thymine are the pyrimidine bases and, guanine and adenine are the purine bases present in DNA.	2. Cytosine and uracil are the pyrimidine bases and, guanine and adenine are the purine bases present in RNA.
3. DNA has double stranded α-helical structure.	3. RNA has single stranded α-helical structure.
4. DNA exists mainly in the nucleus of the cell.	4. RNA exists mainly in the cytoplasm of the cell.
5. DNA molecules are very large in size; their molecular masses may vary from 6 million to 16 million.	5. RNA molecules are relatively small in size with molecular masses ranging from 20,000 to 40,000.

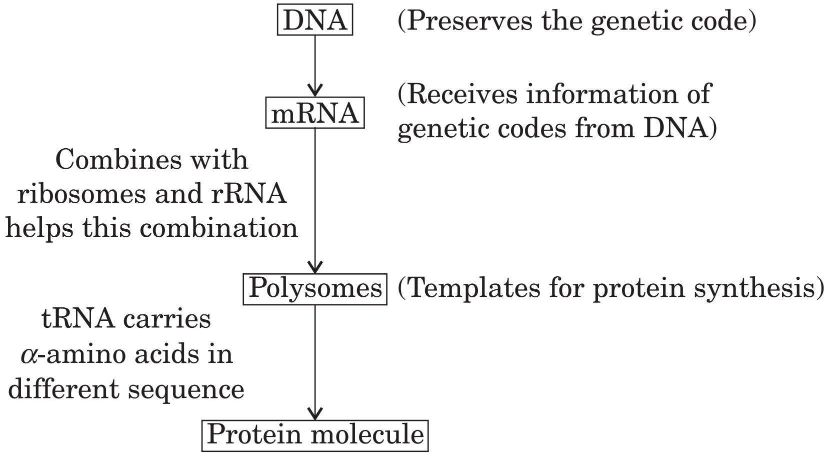
6. DNA possesses the unique property of replication.	6. Replication does not usually takes place in RNA.
7. DNA encodes an organism's entire hereditary information and controls the growth and cell division.	7. Protein synthesis is controlled by RNA

10.3.1.3 Functions of Nucleic Acids

The two nucleic acids DNA and RNA play a very important role in the existence of all forms of life. Their functions are given below:

DNA (i) It acts as a template for RNA which controls the synthesis of proteins. (ii) The entire structural and functional make up of the cell is controlled by DNA. (iii) Self replication (ability to build another molecule of its own kind) is a unique property of DNA and hence it is responsible for passing on heredity trait from one generation to another. (iv) When DNA is exposed to electromagnetic radiations (e.g., X-rays, UV rays, γ-rays) and some specific chemicals, it undergoes mutation (change in the sequence of heterocyclic bases along the strands). This change is reflected in the subsequent generations.

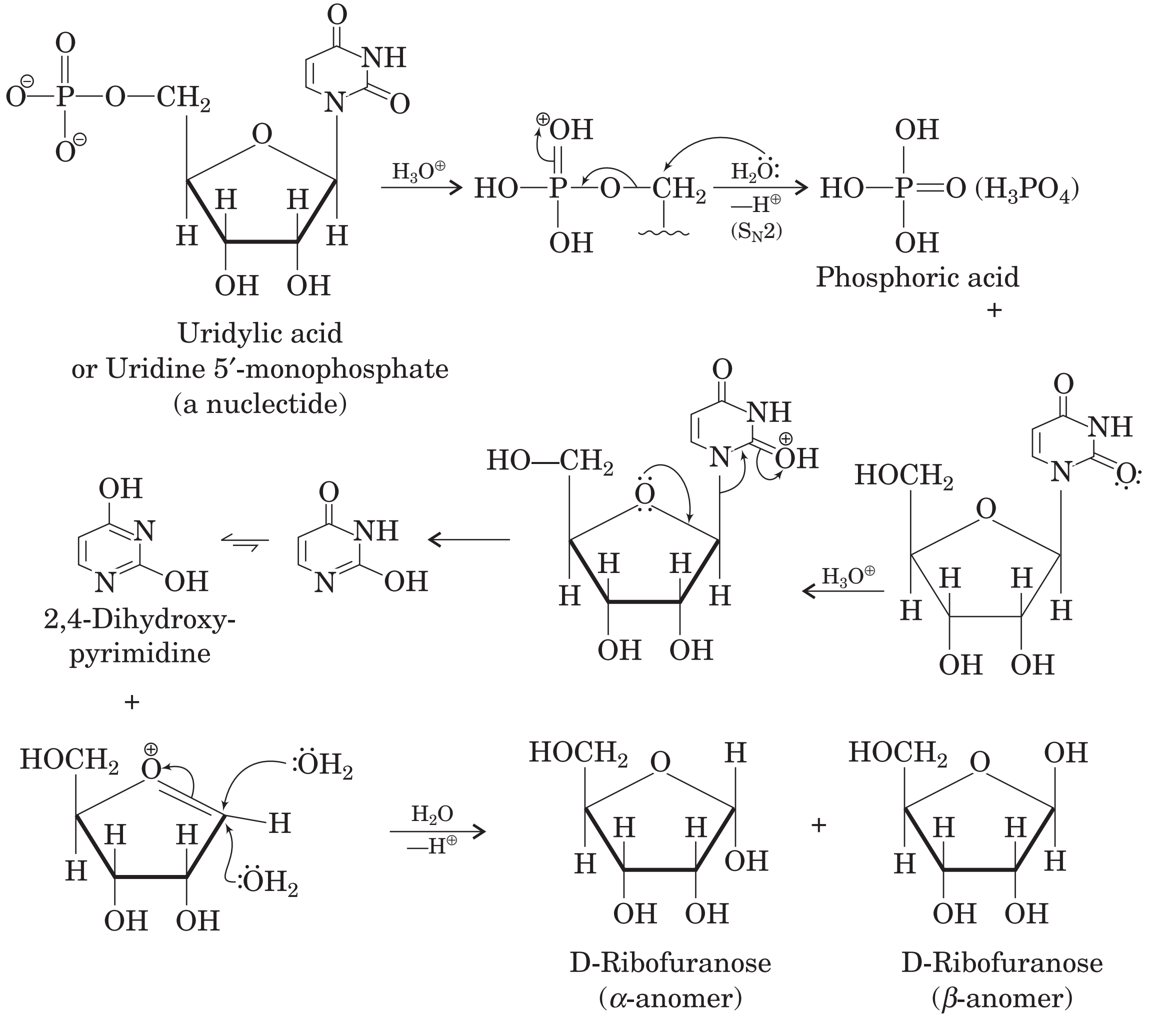
RNA (i) Synthesis of proteins are controlled by RNA. In fact, RNA molecules are responsible to maintain the α-amino acid sequence in protein molecules during their syntheses. There are three different types of RNA molecules. They are designated as mRNA (messenger RNA), rRNA (ribosome RNA) and tRNA (transfer RNA). The job of each type of RNA is different. The scheme for protein synthesis is given below:


DNA
(Preserves the genetic code)
mRNA
(Receives information of genetic codes from DNA)
Combines with ribosomes and rRNA helps this combination
Polysomes
(Templates for protein synthesis)
tRNA carries α-amino acids in different sequence
Protein molecule

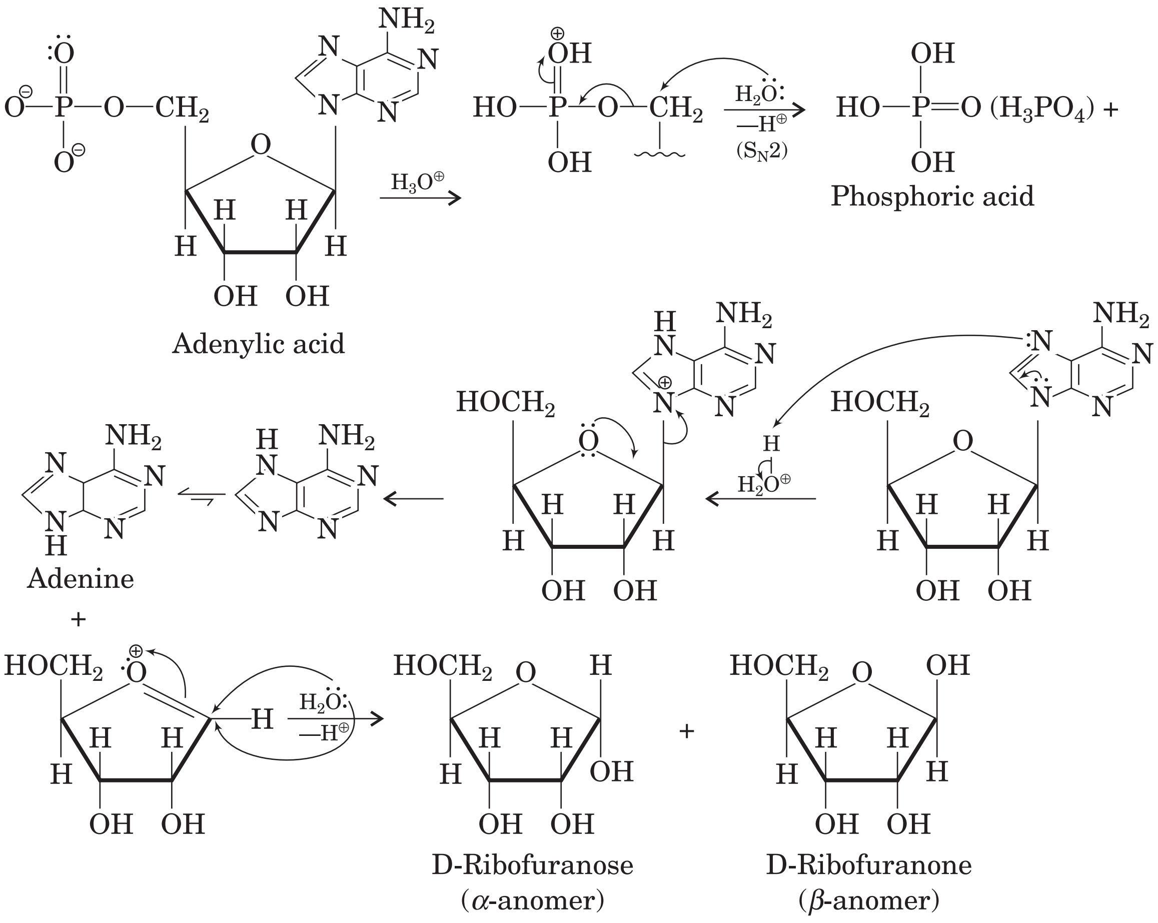
(ii) The process of learning and memory storage is controlled by RNA.

10.3.2 Mechanism for Acid-catalyzed Hydrolysis of Nucleotides (both pyrimidine and purine types)

10.3.2.1 Mechanism for acid-catalyzed hydrolysis of the ribonucleotide uridylic acid or uridine 5-monophosphate (which contains a pyrimidine base)



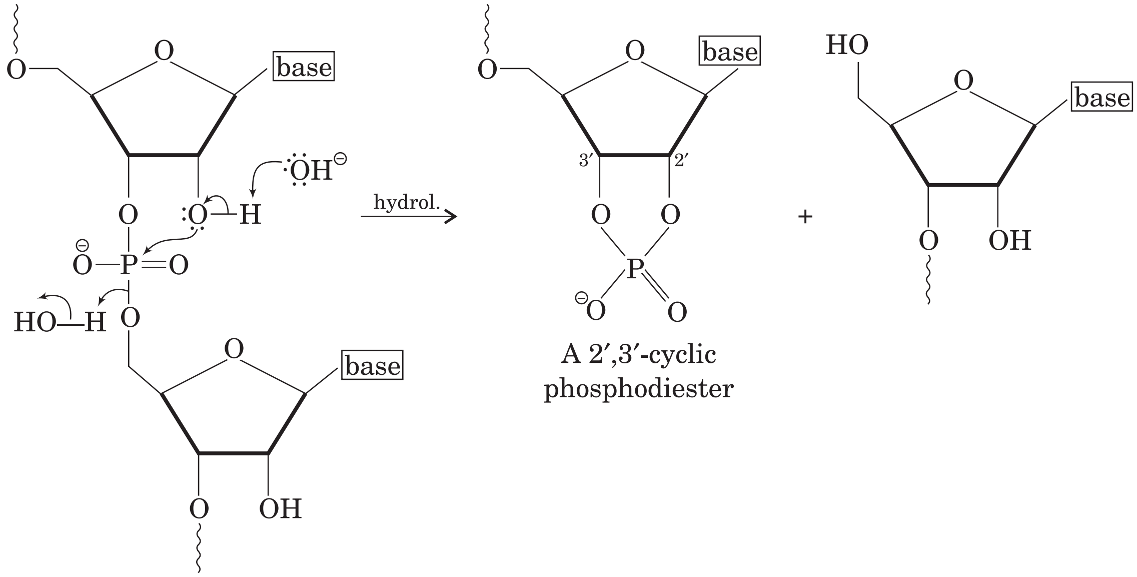
10.3.2.2 *Mechanism for acid-catalyzed hydrolysis of the ribonucleotide adenylic acid or adenosine 5′-monophosphate (which contains a purine base)*



10.3.3 Alkaline Hydrolysis of RNA and DNA

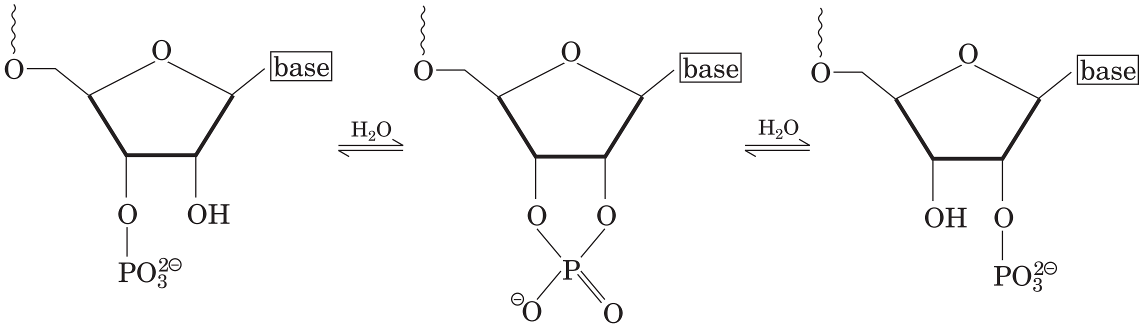
RNA is susceptible to base-catalyzed hydrolysis because the ribose sugar in RNA has a hydroxyl group at 2′ position. This feature makes RNA chemically unstable compared to DNA, which does not have this 2′OH group and thus is not susceptible to base-catalyzed hydrolysis. In fact, base takes up a proton from the 2′ OH group of RNA and the incipient alkoxide attacks the phosphorus atom of the phosphodiester linkage and causes ready hydrolysis due to intramolecular nucleophilic attack. The resulting 2′, 3′-cyclic phosphate group hydrolyzes to either 2′ or 3′ phosphate.

Mechanism of alkaline hydrolysis:



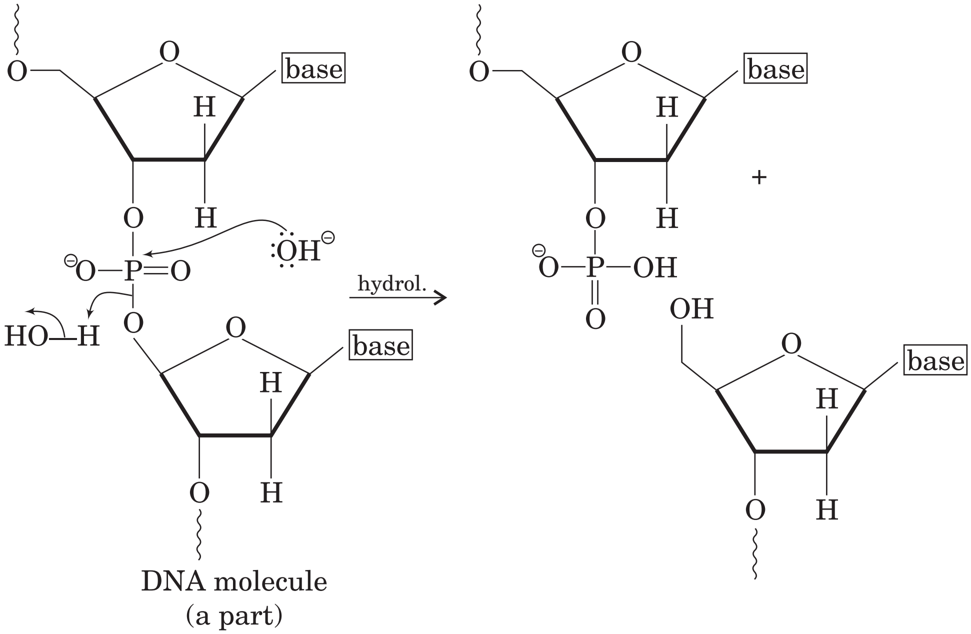
A 2′,3′-cyclic phosphodiester

RNA molecule
(a part)



Phosphodiester

Due to absence of 2′ OH group in DNA, it undergoes normal alkaline hydrolysis of the phosphodiester linkage. Therefore, the rate alkaline hydrolysis of DNA is much slower than that of RNA.



SOLVED PROBLEMS

1. What are called nucleic acids?

Solution Nucleic acids are high molecular-mass biopolymers that can be hydrolyzed to a mixture of heterocyclic bases, a pentose, and phosphoric acid. Sometime they remain combined with proteins as nucleoproteins, and are found to be present in the nucleus and cytoplasm of all living cells.

2. Mention the components of DNA. [C.U. 2011]

Solution The components of DNA (deoxyribonucleic acid) are: (i) the sugar 2-deoxyribose (ii) a phosphate group, and (iii) a heterocyclic base which is either a purine [adenine (A) or guanine (G)] or a pyrimidine [cytosine (C) or thymine (T)] derivative.

3. What do you mean by the terms nucleosides and nucleotides? Show the H-bonding in G–C base-pairing in DNA double helix. [C.U. 2010, 2014]

Solution Nucleosides are β-glycosides of D-ribofuranose or 2-deoxy-D-ribofuranose whose aglycones (the purine or pyrimidine bases) are bonded to C-1 of the sugar. A nucleotide, on the other hand, is a nuelcoside esterified at a sugar —OH group to a phosphate group. Therefore, it consists of a base, a sugar, and a phosphate group.

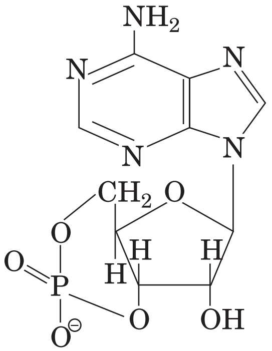
Nucleoside = base + sugar

Nucleotide = base + sugar + phosphate

See also **article no. 10.3.1** for G–C base-pairing.

4. What is called cyclic AMP? Explain why it undergoes alkaline hydrolysis to yield 3′-adenylic acid (adenoside 3′-phosphate) rather than 5′-adenylic acid.

Solution Adenosine 3′, 5′-monophosphate (an important nucleotide) is commonly known as cyclic AMP.



Cyclic AMP

Since its reaction with aqueous NaOH takes place through an S_N2 mechanism, nucleophilic attack occurs preferentially at the less crowded primary 5′-carbon atom rather than at the relatively more crowded secondary, 3′-carbon atom and as a result, 3′-adenylic acid is obtained as the major product.

5. **How does ribonucleic acid (RNA) differ from deoxyribonucleic acid (DNA) with respect to its structure and function? [C.U. 2011]**

Solution RNA differs from DNA in two principal ways.

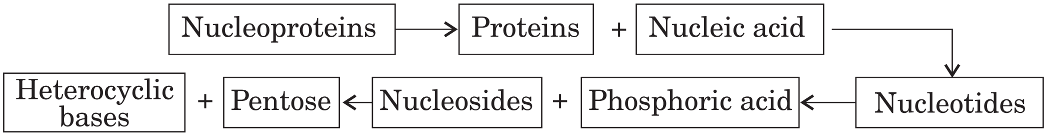
(i) The sugar (pentose) is D-ribose rather than 2-deoxy-D-ribose.
(ii) The pyridimine base uracil (U) replaces the pyrimidine base thymine (T).

See also **article no. 10.3.1.3** (functions of nucleic acids).

6. **What do you mean by nucleoproteins? Show the four stages involved in the hydrolytic degradation of nucleoproteins.**

Solution A class of conjugated proteins which contains nucleic acids as prosthetic groups and which determines the heredity in living organisms are called nucleoproteins.

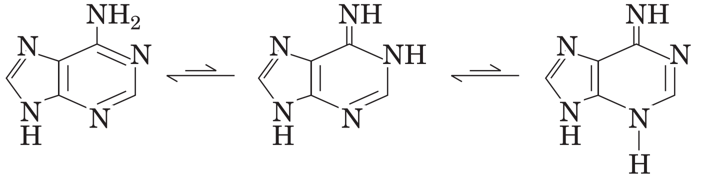
The four stages in the hydrolytic degradation of nucleoproteins are shown below:



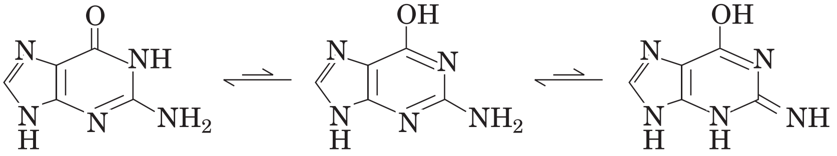
7. **Write structures of two other tautomeric forms of each of the five nucleic acid bases.**

Solution

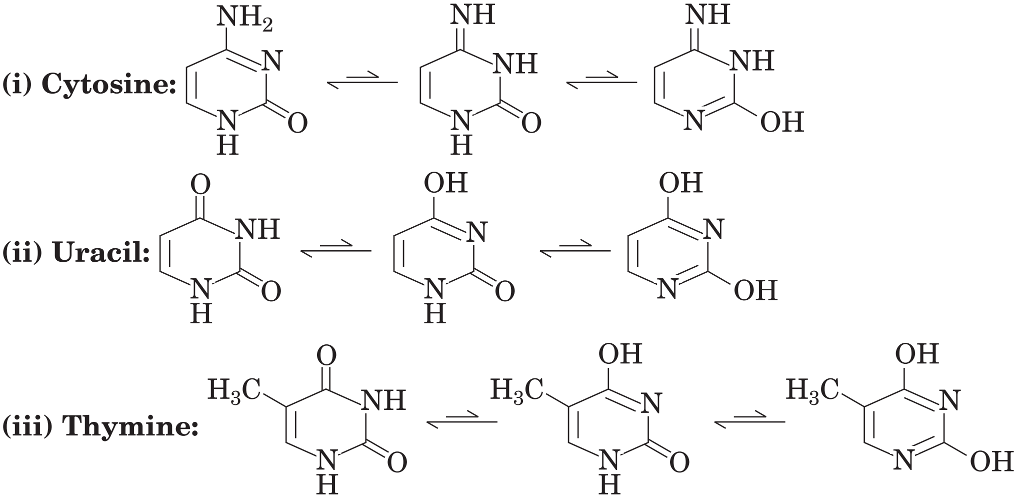
(i) Adenine:



(ii) Guanine:



(The two purine bases)

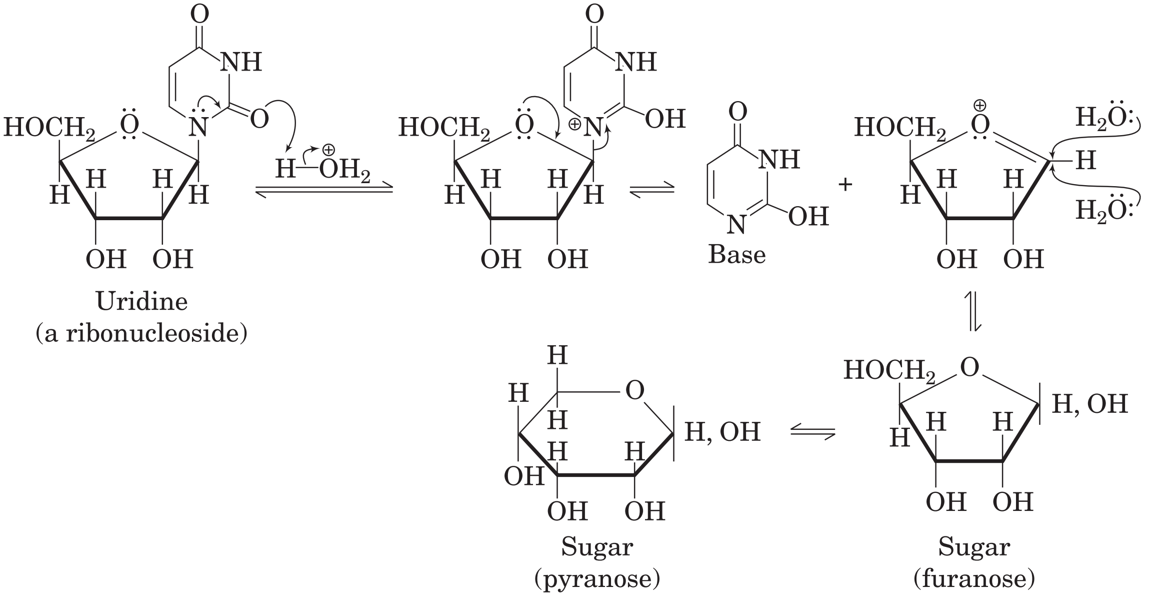


(the three pyrimidine bases)

Despite the added stabilization of an aromatic ring (2nd and 3rd structure of the purine bases and 3rd structure of the pyrimidine bases), these compounds prefer to adopt amide-like structure and that is due to greater thermodynamic stability (bond energy).

8. **Explain why nuelcosides are stable in dilute base, but undergo ready hydrolysis in aqueous acid. Suggest a reasonable mechanism for the hydrolysis.**

Solution Since the nucleosides have *N*-glycosidic linkage, they undergo rapid hydrolysis in aqueous acid because in acid, the base undergoes protonate and becomes a good leaving group. In alkali, hydrolysis does not take place because the leaving group in this case is a strong (unstable) base and cannot be separated from the sugar part.



The sugar in furanose form immediately changes into the stable pyranose form.

9. How can the process of denaturation occurs when a solution of DNA is heated?

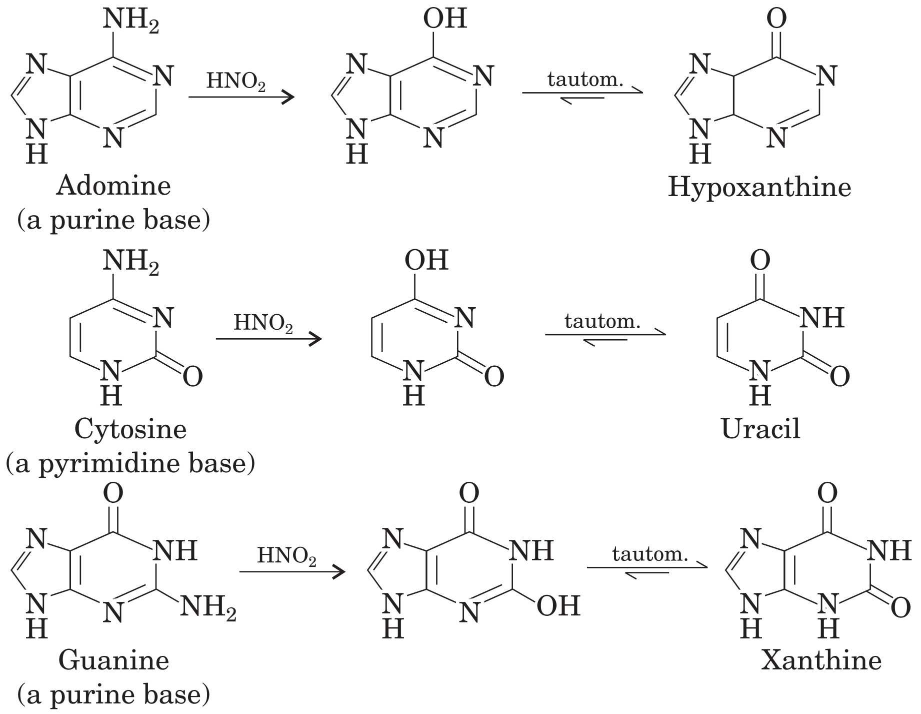
Solution The hydrogen bonds between the paired bases and the van der Waals forces of attraction that hold the stacked base-pairs are disrupted. As a consequence, the ordered conformation breaks and the double helix undergo dissociation into random, disordered coils. In this way, denaturation of DNA occurs when it is heated.

10. How does a change in the sequence of bases in DNA cause a mutation? What do you mean by a silent and a lethal mutation?

Solution A change in a single base-pair in DNA causes substitution of a different α-amino acid in the protein being synthesized. This leads to mutation. When the substitution of a different amino acid does not significantly change the normal activity of the protein, this is called a silent mutation. However, when the substitution leads to the formation of a defective harmful protein or when due to such substitution the production of an essential protein is hampered, it is called a lethal mutation.

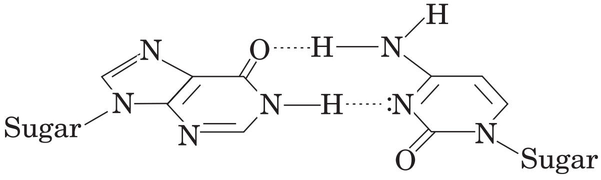
11. Account for the mutagenic activity of nitrous acid (HNO_2) on deoxyribonuclic acid (DNA).

Solution Nitrous acid converts the —NH_2 group of the heterocyclic bases adenine, guanine and cytosine to an —OH group through diazotization. The resulting bases undergo base pairing in a different sequence, thereby forming an abnormal DNA which changes the genetic code and leads to possible mutations.



12. In DNA, adenine usually pairs with thymine. However, hypoxanthine, obtained from adenine by the action of nitrous acid, pairs with cytosine. Show the H-bonds of a hypoxanthine-cytosine base-pair.

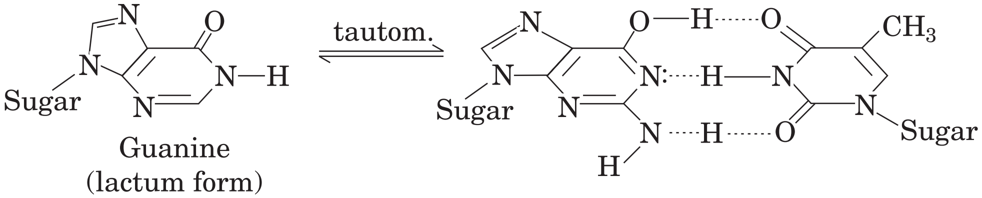
Solution



Hypoxanthine Cytosine

13. If the base guanine tautomerizes to the abnormal lactim form, it pairs with thymine instead of cytosine. Show the hydrogen bonds in this abnormal base-pair.

Solution



Guanine
(lactum form)

Guanine
(lactim form)

Thymine

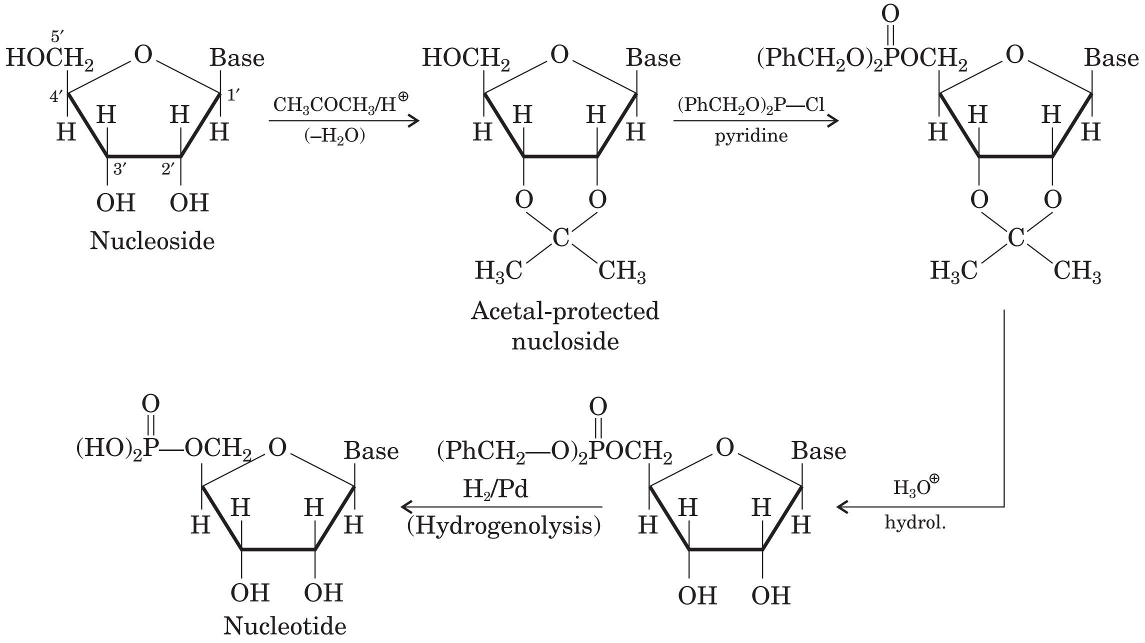
14. Explain why the compounds like active halides (e.g., CH_3I), epoxides, nitrosamines possess carcinogenic behaviour. Is benzo[*a*]pyran a carcinogen?

Solution Carcinogenic (cancer-producing) compounds possess mutagenic activity and this is because by altering the base sequence they bring about a change in the protein being synthesized and a corresponding change in biological function. The O and N atoms (the nucleophilic sites) of the heterocyclic bases undergo alkylation by these three classes of compounds. The alkylated bases causes unusual base pairing leading to mutation. This explains why these compounds possess carcinogenic behaviour.

BAP itself is not a carcinogenic compound. However, during partial metabolism it becomes converted to an epoxide derivative which can act as an alkylating agent. Therefore, BAP is a carcinogen.

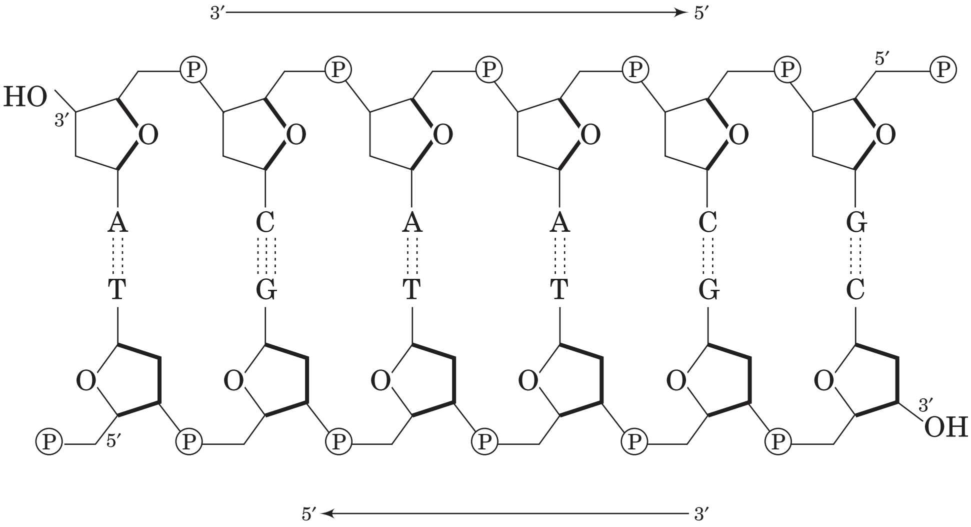
15. How can nucleosides be converted to nucleotides?

Solution Conversion of a nucleoside to a nucleotide may be carried out by using the important phosphorylating agent dibenzyl phosphochloridate $[(PhCH_2O)_2\overset{\overset{\displaystyle O}{\|}}{P}Cl]$. Specific phosphorylation of the 5′–OH group can be achieved if the 2′– and 3″–OH groups of the nucleoside are protected by an isopropylidine group through the formation of a cyclic acetal using acetone.



16. Show the complementary base pairing in DNA by a suitable diagram.

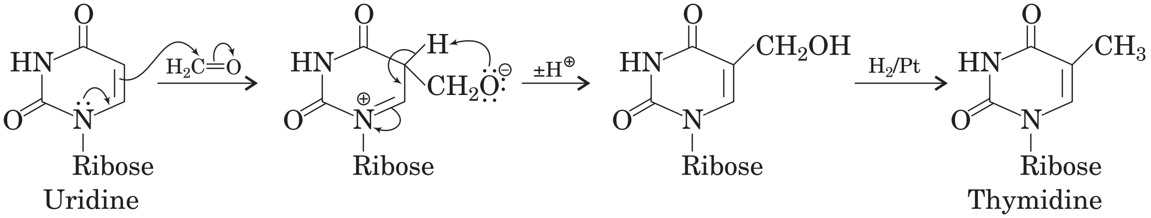
Solution



Complementary base pairing in DNA

17. How would you convert uridine to thymidine?

Solution



18. What is meant by specific base-pairing is double helix structure of a DNA molecule? Why the other base-pairings have not been observed in DNA double helix structure? [C.U. 2014]

[**Hint:** See **article no. 10.3.1** (secondary structure)]

STUDY PROBLEMS

1. What do you mean by the terms dinucleotide, oligonucleotide and polynucleotide? Give examples of polynucleotide.

[**Hint:** A dinucleotide contains two nucleotide subunits, an oligonucleotide contains 3 to 10 subunits, and a polynucleotide contains many subunits.]

2. Indicate whether each functional group of the five heterocyclic bases in nucleic acids can function as a hydrogen bond accepter, a hydrogen bond donor, or both.

3. If one of the strands of DNA has the following sequences of heterocyclic bases running in the 3′→5′ direction.

3′ – T – A – C – G – T – C – A – T – G – C – G – 5′

(a) What is the sequence of bases in the complementary strand?

(b) What base is closest to the 3′-end of the complementary strand?

[**Hint:** (a) 5′ – A – T – G – C – A – G – T – A – C – G – C – 3′]

4. A 2′, 3′-cyclic phosphodiester undergoes hydrolysis to yield a mixture of nucleotide 2′- and 3′- phosphates. Propose a mechanism for this reaction.

5. Why do DNAs from various sources possess different melting temperatures (T_ms)?

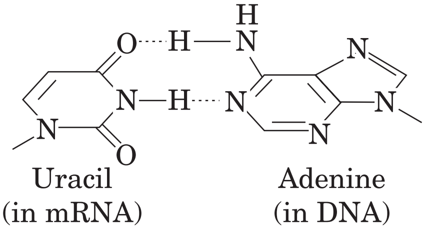
[**Hint:** DNAs have different amounts of G : C and A : T base-pairs, and the former, due to greater number of H-bonds between them, confers greater stability to the double helix. Thus, the higher the G : C content, the higher the T_m.]

6. How many 3′,5′ phosphodiester linkages are expected to be present in a linear polynucleotide chain containing 25 nucleotide units.

[**Hint:** A phosphodiester linkage connects each nucleotide to the adjacent one; therefore, the total number of such linkage is always less than the number of nucleotide units. Phosphates at the 3′ or 5′ end do not constitute phosphodiesters. Therefore, the number of phosphodiester linkage is 24.]

7. Show how the keto-form of uracil in mRNA can pair with adenine in DNA through H-bond formation.

[**Hint:**



]

8. The two strands of DNA in double helix are not identical, but complementary. Explain.

9. What are the functions of nucleic acids in human body?

10. Mention four differences between DNA and RNA.

11. What structural feature of DNA accounts for the ratio of G to C and A to T being close to unity?

12. Give the structural formulas for (i) adenosine 5′-triphosphate (ATP), and (ii) deoxyuridine 3′-monophosphate dUMP).

13. Sodium nitrite ($NaNO_2$), a common food preservative, may cause mutations in an acidic environment by converting cytosines to uracils. Explain how this can take place.

14. Write the names and structures of any two purine and pyrimidine bases related to nucleic acids. **[C.U. 2013]**

[**Hint:** See **article no 10.3.1.**]

15. Draw the structure of the following compounds:

(i) A nucleoside containing a base unit found only in RNA and not in DNA, (ii) a nucleotide containing a base unit present in DNA which is complementary to Thymine. **[C.U. 2015]**

[**Hint:** (i) Uridine (ii) Adenylic acid. See **article no. 10.3.1.**]

16. Which cytosine in the following DNA strand may cause maximum damage to the organism if it undergoes deamination?

$$5' - A - T - G - T - C - G - C - T - A - A - T - C - 3'$$

17. Draw the structure of a four-residue segment of DNA with the following sequence:

$$5' - C - A - T - G - 3'$$

18. Draw the structure of the following nucleotides:

(a) Guanosine triphosphate (GTP) (b) dCMP

(c) cGMP (d) AMP (e) TMP

19. Explain why the nitrous acid-induced mutation of cytosine to uracil is more easily repaired in DNA than it is in RNA.

20. Polyribonucleotides are quite readily hydrolysed by aqueous alkali but polydeoxyribonucleotides are not. Explain this observation.

21. What is called the Chargaff's rule? Does Chargaff's rule apply only to double-stranded DNA, or would it also apply to individual strand if the double helical strand were separated?

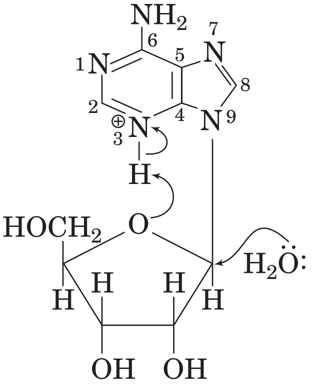
[**Hint:** Erwin Chargaff's discovered that DNA contains equimolar amount of guanine and cytosine and also equimolar amounts of adenine and thymine. This is known as the *Chargaff's rule*. This rule is applicable only to double-stranded DNA.]

22. DNA and RNA bases belong to two different classes of heterocycles. What are these classes? Predict whether the relative sizes of two classes of heterocyclic bases play any role in the chemical regularity of the DNA molecule?

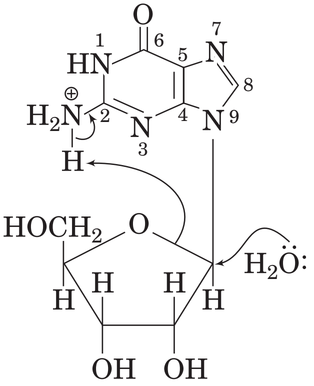
23. When RNA is hydrolyzed, no relationship has been found among the quantities of the four bases obtained similar to that observed for the bases obtained from DNA. What can be inferred from this observation about the structure of RNA?

24. Identify the H-bonds between the conjugate base pairs of DNA. **[C.U. 2012]**
[**Hint:** See **article no. 10.3.1**]

25. Write down the structure of adenosine and guanosine. Explain why guanosine is hydrolysed more rapidly than adenosine. **[C.U. 2012]**
[**Hint:** See **article no. 10.3.1** (nucleotides and nucleosides).



Adenosine



Guanosine

That guanosine is hydrolysed more rapidly than adenosine is due to effective intramolecular catalysis involving the –$\overset{\oplus}{N}H_3$ group at the 2-position. This –NH_2 group is less basic than the 3-imino group (in both purines) and so proton release from –$\overset{\oplus}{N}H_3$ is easier.]

25. Mention the names of different types of RNAs and their functions. **[C.U. 2012]**
[**Hint:** See **article no. 10.3.1.3.**]

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Index

Index Guide: Alphabetization is by the "word" method, which uses the first term in a compound term; hyphenated terms are treated as one word. Leading numbers, Greek letters, and other descriptors (*E*, *cis*, *tert*, etc.) are ignored unless they alone determine the order.

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